ORIGINAL ARTICLE

Fasting insulin serum levels and psychopathology profiles in male schizophrenic inpatients treated with olanzapine or risperidone

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Abstract

OBJECTIVE: Recent studies have suggested that higher insulin levels are associated with better psychopathology profiles in cross-sectional samples of patients with schizophrenia. This study examines whether drug-induced fasting insulin changes between third and eight week of treatment are related to clinical improvement in non-diabetic patients receiving the atypical neuroleptics: risperidone or olanzapine.

METHODS: non-diabetic men with a diagnosis of schizophrenia according to the DSM-IV diagnostic classification were recruited from psychiatric inpatient units. Following a drug-free period, neuroleptic treatment was initiated (risperidone n=36, olanzapine n=35) and doses were adjusted to achieve maximal clinical efficacy. All patients were hospitalized throughout the study. Initial and final evaluations of serum insulin levels and psychopathology (assessed with the Positive and Negative Syndrome Scale, PANSS), were carried out at weeks 3 and 8 after the onset of treatment, respectively.

RESULTS: There were no differences between and within the risperidone and olanzapine groups in changes of serum insulin level between the third and eighth week of treatment. In the olanzapine group, Pearson correlation analysis revealed a significant negative correlation between changes in fasting serum insulin levels and the PANSS-Total, Positive and General Psychopathology subscale scores. Only improvement in the PANSS-Negative Symptom subscale score was not correlated with insulin level change between the third and eighth week of treatment. In the risperidone group, correlations between PANSS subscales scores and the corresponding serum insulin levels change were positive, albeit statistically non-significant. In both groups the improvement in PANSS-Total scores was not correlated with changes in BMI.

CONCLUSION: Olanzapine-related changes in endogenous fasting insulin levels were correlated with clinical improvement in acutely ill non-diabetic schizophrenic patients. Because the interesting linkage between insulin and positive and negative symptoms could be an epiphenomenon, randomized studies are needed to further explore the role of insulin in therapeutic responses in patients with schizophrenia.

INTRODUCTION

Studies of brain glucose metabolism suggest that the uptake of glucose by central nervous system (CNS) tissues is independent of peripheral insulin levels; therefore, the brain is characterized as being insulin-insensitive. However, Hoyer *et al.* (1996) demonstrated that hippocampal glucose metabolism is sensitive to the application of exogenous insulin and that this sensitivity is due to insulin receptors. Thus, insulin can promote glucose utilization in some brain areas (Hoyer *et al.* 1996). Several studies have found high levels of insulin receptors in the CNS. Most of these receptors are located in the olfactory bulb, cerebral cortex, hippocampus, cerebellum and hypothalamus (Unger *et al.* 1989; Zhao *et al.* 2001).

The origin of brain insulin is still controversial. Studies have indicated that insulin is transported from the periphery to the CNS (Woods *et al.* 1985). There is also some evidence for synthesis of insulin or insulin related molecules in some types of neuronal tissue (Devaskar *et al.* 1994; Schechter *et al.* 1988). Recent studies have suggested that insulin may modulate cognitive activity by acting in the CNS. For example, Benedict *et al.* (2011) demonstrated beneficial effects of intranasal insulin on memory functions both in healthy humans and in patients with cognitive impairments, such as Alzheimer's disease (see also Lang *et al.* 2010; Stone *et al.* 2011). These mechanisms may be independent of insulin's effects on glucose uptake. The pathogenesis of some neurological and psychiatric disorders, and their associated cognitive deficits, may be related to insulin levels or insulin sensitivity.

There are also suggestions of a relationship between glucose regulation and schizophrenia (Beaulieu 2012; Freyberg *et al.* 2010; Keri *et al.* 2011). It has been proposed that the psychopathology of schizophrenia is best explained as a diabetic brain state (Holden *et al.* 1994). Schizophrenic patients exhibit impaired glucose regulation, poor memory and attention, and an oral glucose load appears to improve their performance in several cognitive tasks (Park 2001). Weston-Green *et al.* (2012) have recently demonstrated associations between the effects of second-generation antipsychotics on glucose metabolism and insulin secretion. Data from a number of studies suggest that drug-induced changes in weight are primarily responsible for treatment–related changes in glucose metabolism (Chiu *et al.* 2010; Zhang *et al.* 2004). It has been established that there is a link between treatment- emergent weight gain caused by first and second-generation drugs and positive therapeutic response (Czobor *et al.* 2002; Lane *et al.* 2003; Meltzer *et al.* 2003). Weight gain and other metabolically adverse events are usually related to elevated insulin secretion (Chiu *et al.* 2010). In a Fan et al.(2006) study, higher fasting serum insulin levels were associated with better psychopathology profiles in acutely ill non-diabetic inpatients with schizophrenia. Fan et al.(2006) suggested that insulin might improve clinical symptoms of schizophrenia by interacting with dopamine and other brain neurotransmitter systems independently of weight gain.

The overwhelming evidence suggest that atypical antipsychotics influence insulin serum levels (Ebenbichler *et al.* 2003; Henderson *et al.* 2005, Melkersson *et al.* 2000; Weston-Green *et al.* 2012). We therefore performed this study to investigate the relationship between endogenous fasting serum insulin levels and the psychopathology profiles of non-diabetic, acutely ill schizophrenic inpatients treated with olanzapine or risperidone. We hypothesized that increases in serum insulin levels between third and eight week of treatment should be positively correlated with symptomatic recovery. To our knowledge, this is the first study directly examining the relationship between the endogenous insulin level changes and the clinical symptomatology of schizophrenia.

METHODS

Patients

We recruited men with diagnoses of schizophrenia according to the DSM-IV diagnostic classification, who were hospitalized in psychiatric inpatient units. All subjects met the following inclusion criteria: a) they had been free of oral antipsychotic medications for at least 3 weeks before the study and free of depot neuroleptics for 3 months; b) they had no history of chronic somatic diseases including diabetes (exclusion criterion: fasting plasma glucose level ≥126mg/dL); c) they did not use anti-diabetic or lipid-lowering therapy. Patients with substance misuse or significant organic brain disease were also excluded. Illness characteristics and demographic data were obtained from clinical interview and medical records. Written informed consent was obtained from each subject after a complete description of the study. The Hospital Ethical Committee approved our study.

Study design

After providing written informed consent, each subject underwent a physical examination and a psychiatric diagnostic evaluation. During the pre-drug (baseline) period, fasting serum glucose levels were assessed in a local laboratory using standard methodologies to exclude patients with undiagnosed diabetes. In eligible subjects, neuroleptic treatment was initiated with doses of risperidone or olanzapine that were adjusted to achieve maximal clinical efficacy. In the course of study, we assessed insulin serum levels and psychopathology profiles twice, at week 3 (initial evaluation) and week 8 (final evaluation) after the onset of the treatment. We chose those particular measurement points because insulin secretion in patients treated with olanzapine display biphasic changes between week 2 and 8 of treatment (Chiu *et al.* 2010). By choosing week 3 as an initial

time point we also eliminated clinical improvement within the first two weeks of treatment determined primarily by individual illness course characteristics (Schennach *et al.* 2012). In the risperidone group, fasting insulin levels were analyzed in 35 subjects at week 3. For 28 of these subjects clinical symptoms were assessed by means of PANSS total and subscale scores. At the final evaluation (week 8), PANSS total and subscale scores were obtained for 34 patients, and fasting insulin levels were analysed in 23 of these subjects. In olanzapine group, the initial and final evaluation of serum insulin levels were analysed in 32 and 23 subjects, respectively, whereas PANSS total and subscale scores were assessed in 16 and 21 subjects, respectively. In 16 subjects treated with risperidone and 10 treated with olanzapine, we were able to compare fasting insulin levels between the two measurement points and correlate them with the clinical symptoms assessed by the PANSS. We were unable to perform assessments on all patients for the following reasons: in 8 cases, we were not able to control overnight fasting, and 16 patients refused to give their blood for laboratory testing at final evaluation.

Hormone assay

The initial and final evaluations of insulin serum levels were performed at weeks 3 and 8 after the onset of the new treatment, respectively. A single fasting morning blood sample was obtained from all patients between 07.00-08.00 h. Patients should not have eaten or taken any medications since the previous midnight. Whole blood was collected and centrifuged to separate serum. Serum insulin levels were measured by radioimmunoassay (INS IRMA, Starr *et al.* 1978). Body weight was assessed twice, at the third and at the eight week of treatment, to the nearest 0.1 kg. Body mass indices (BMI) were calculated using the following formula: BMI=weight(kg)/[height(m2)].

Clinical assessment

To evaluate positive and negative symptoms and the general psychopathology associated with schizophrenia, we used the 30-item Positive and Negative Syndrome Scale (PANSS, Kay *et al.* 1987). Each item is rated on a scale from 1 (symptom not present) to 7 (symptom extremely severe). The sum of the 30 items is defined as the PANSS total score and ranges from 30 to 210. The initial and final evaluations were performed at weeks 3 and 8 after the onset of the new treatment. They were performed by one rater who was blind to the blood assay results.

Statistical analyses

All data were log transformed prior to statistical analyses. Assumptions of the parametric tests were verified before the tests were performed (Sokal and Rohlf 1995). Between-treatment differences in the means of patients' ages, ages at first hospitalization, body masses and fasting serum concentrations of insulin and glucose, as well as in total PANSS and its subscales were tested by t-test analysis. Within-drug changes and correlations of PANSS scores, BMI and serum insulin were tested with paired t-tests and Pearson product-moment correlation. Descriptive characteristics are presented as the means ± SD. Statistical significance was defined as p=0.05 unless otherwise stated.

RESULTS

Baseline characteristics of the study groups

The baseline characteristics of the risperidone and olanzapine treatment groups are presented in Table 1. There were no statistical between-group differences in age, age at first hospitalization or body mass at the initial and final evaluations. Likewise, baseline measures of fasting serum concentrations of glucose showed no significant differences between the investigated groups.

PANSS scores, BMI and serum insulin level at 3 and 8 week of treatment

There were no statistically significant between-treatment differences in the total, positive, negative or general PANSS subscale scores or BMI at the initial (week 3) and final evaluations (week 8, Table 1). Likewise, the investigated groups did not differ in their mean serum insulin levels at the third and eighth week of treatment (Table 1). In both treatment groups, the body masses of subjects increased significantly between the initial and final evaluations (paired t-test, risperidone group p<0.001; olanzapine group, p=0.003). Within both treatment groups, there were no significant changes in serum insulin levels.

In subjects treated with risperidone, total PANSS scores and Positive Psychopathology subscale scores significantly decreased over the course of treatment (paired t-test, p=0.02 and p=0.002, respectively). On the other hand, there was no significant change on the Negative and General subscales (paired t-test p=0.4 and p=0.08, respectively). Within the olanzapine treatment group, there were statistically significant decreases in total PANSS scores (p=0.002), and Positive (p=0.01), General (p=0.004) as well as Negative (p=0.005) subscale scores.

Within the olanzapine treatment group, serum insulin changes were inversely correlated with changes in PANSS-Total, Positive and General, but not Negative Psychopathology subscale scores (Figure 1). In contrast, in the risperidone study group, no correlations between PANSS subscale scores and corresponding serum insulin level changes were significant. Notably however, and unlike in the olanzapine-treated group, all correlations between insulin levels and PANSS scores were positive.

In both investigated groups, the improvement in PANSS-Total score was not correlated with the corresponding changes in BMI (risperidone: r=0.36, p=0.15, n=17, olanzapine: r=0.03, p=0.91, n=14).

Tab. 1. Descriptive statistics of study groups at baseline, at the third and eight week of treatment.

CHARACTERISTICS	OLANZAPINE			RISPERIDONE			
BASELINE	**Range**	**Mean**	**SD**	**Range**	**Mean**	**SD**	***p*-value**
Age (years)	20–60	33.2	10.8	19–55	32.8	9.6	0.88
First hospitalization (years)	13–48	24.9	7.2	15–47	25.7	7.7	0.62
Fasting glucose (mg/dL)	62–113	90.9	11.4	72–116	92.0	10.1	0.69
WEEK 3							
Medication dose (mg)	5–30	17.1	6.7	2–7	4.7	1.3	<.0001
Fasting serum insulin (μIU/L)	3.4–20	9.1	3.7	3.4–24.6	10.2	4.6	0.27
PANSS total	46–148	87.6	20.5	50–141	93.7	23.9	0.29
PANSS positive	7–32	18.4	6.7	7–34	20.4	6.8	0.24
PANSS negative	7–42	23.2	5.8	7–46	24.6	7.7	0.40
PANSS general	26–74	46.1	10.3	27–74	48.6	12.3	0.37
Weight (kg)	50–113	79.3	15.5	56–116	76.1	11.8	0.32
BMI (kg/m^2)	17.3–33.4	25.2	3.9	18.1–28.7	23.6	2.9	0.08
WEEK 8							
Medication dose (mg)	5–30	15.9	6.2	2–8	4.3	1.5	<.0001
Fasting serum insulin (μIU/L)	3.8–17.3	9.8	3.4	3.5–26.5	10.9	5.6	0.41
PANSS total	49–97	74.4	15.5	35–115	80.1	19.5	0.33
PANSS positive	8–25	15.1	5.0	7–25	15.3	5.0	0.89
PANSS negative	11–28	20.3	4.4	7–33	22.4	7.0	0.26
PANSS general	25–54	39.1	8.1	21–57	42.4	9.9	0.27
Weight (kg)	58–115	82.9	15.7	63–121	81.5	12.2	0.73
BMI (kg/m^2)	19.8–36.8	26.5	4.3	20.3–31.7	25.4	2.9	0.32

DISCUSSION

In contrast to the results reported by Chiu *et al.* (2010) we did not find any significant changes in the mean insulin levels over the course of study treatment. However, our study shows that individual increases in the serum insulin levels between third and eight week of olanzapine treatment were correlated with an improvement of psychopathological symptoms (expressed as a reduction of the respective PANSS scores), especially those evaluated as the positive and general symptoms of schizophrenia. Conversely, in the risperidone group, none of the correlations between PANSS subscale scores and serum insulin levels were statistically significant: if any relationship was present, an increase in insulin levels was correlated with worsening of psychopathology profiles.

These interesting drug-dependent differences in the linkage of insulin level changes and corresponding changes in symptomatology are puzzling, because olanzapine, but not risperidone treatment is associated with insulin resistance (Ader *et al.* 2005). Nevertheless, according to Fan *et al.* (2006), insulin resistance in the central nervous system may not necessarily accompany peripheral insulin resistance. Fan et al.(2006) suggested that insulin might affect the clinical manifestations of schizophrenia, and these effects are mainly due to insulin's modulating effect on dopamine receptors. Insulin modulates CNS concentrations of neurotransmitters, such as acetylcholine, norepinephrine and dopamine (Figlewicz, *et al.* 1993 (a); Figlewicz, *et al.* 1993(b); Kopf *et al.* 1999; Robertson *et al.* 2010; Woods *et al.* 1996). Peptides derived from insulin may also strongly regulate dopamine transporter activity (Liu *et al.* 2001). Furthermore, dopamine and insulin may exert reciprocal regulation (Chen *et al.* 2005; Figlewicz *et al.* 1994). Alloxan or streptozotocin-treated rats (hypoinsulinaemic-diabetic) showed increased striatal-dopamine binding when they were given insulin (Murzi *et al.* 1996). Studies on animals have therefore reinforced the observations that dopaminergic drugs influence insulin production, insulin resistance, and glycemic control. For example, the intracerebroventricular delivery of bromocriptine, a potent D2 receptor agonist, improved insulin sensitivity in hamsters (Luo *et al.* 1999). Although the striatal dopamine system has traditionally

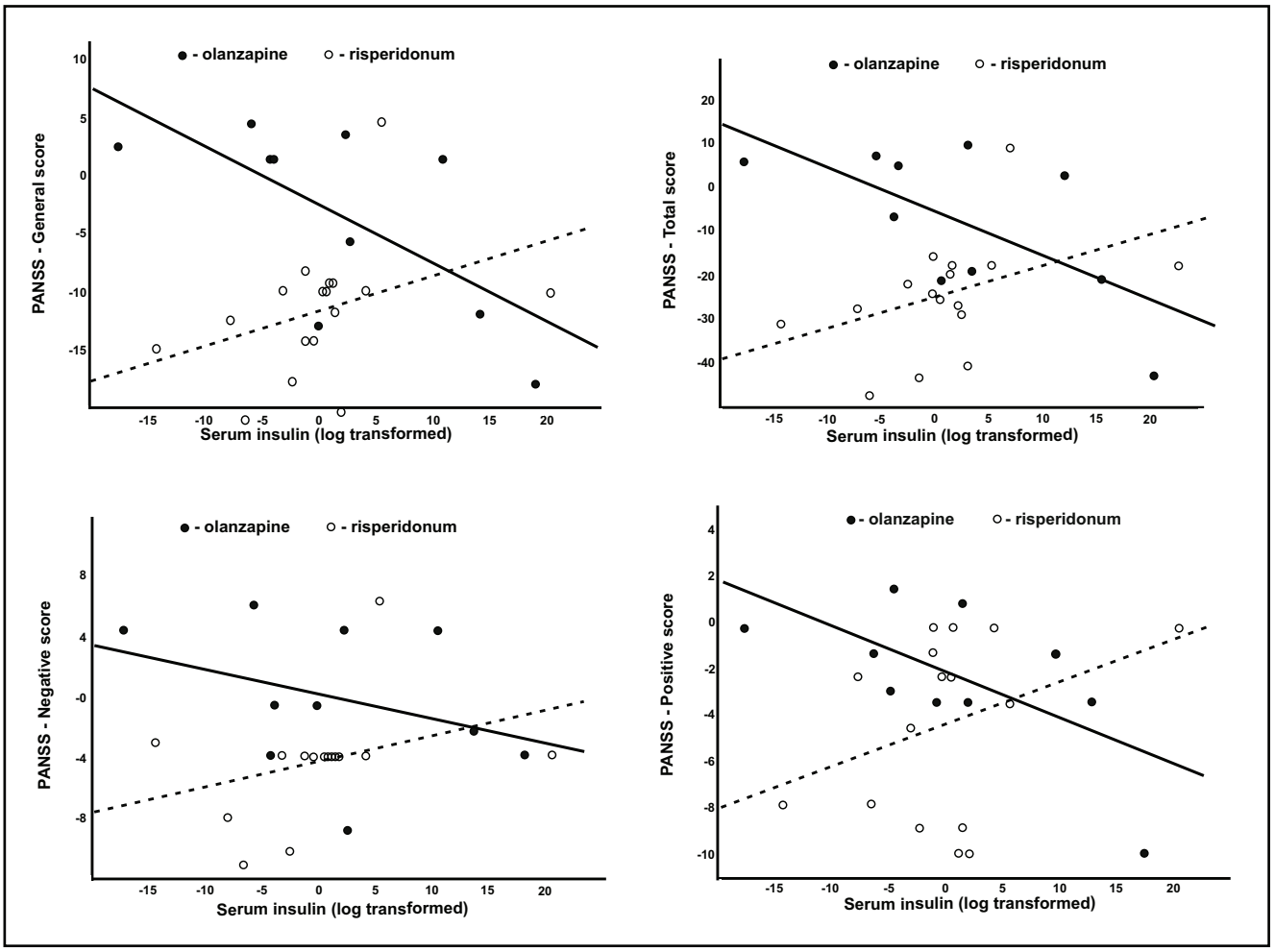

Fig. 1. Correlations between olanzapine (solid circles and solid lines) and risperidone (hollow circles and dashed lines) related changes of endogenous insulin level (log transformed) and the psychopathology measures (PANSS subscales) between the third and eighth week of treatment.

been thought to form circuits that participate in motor coordination (Yang *et al.* 2003), this system may also be involved in the integration of cognitive activities and reward responses through the corticothalamic-basal-ganglia-cortical loop (Chen *et al.* 2005).

Atypical antipsychotic drugs differentially impact a number of neurotransmitter systems including dopamine (Nyberg *et al.* 1997). It is well established that risperidone is a more potent dopamine antagonist than olanzapine (Bymaster *et al.* 1996). We suggest that between-drug differences in antagonism of dopamine receptors may plausibly explain biological basis of the inverse correlation between changes in insulin levels and clinical improvement in our patients treated with olanzapine. In patients treated with risperidone, strong dopamine antagonism may decrease insulin brain sensitivity; under olanzapine administration, endogenous insulin serum increases may exert beneficial effects on dopamine receptor sensitization, and thus positively affect clinical manifestations of schizophrenia. Stimulation of insulin receptors triggers phosphorylation of tyrosine receptor kinase and activation of a downstream signal transduction pathway that leads to protein kinase B/Akt. Akt is a multifunctional kinase that regulates anti-apoptotic activities, cellular growth and glucose metabolism (Chang *et al.* 2003). A study by Zhao *et al.* (2006) provides evidence of a link between insulin receptor dysfunction and suppressed Akt signaling in schizophrenia. According to Altar *et al.* (2008) activation of insulin/IGF-1 receptors alters genes associated with metabolic and synaptic functions in a manner reciprocal to their changes in schizophrenia. Winkel *et al.* (2011) reported that genetic variation in AKT1 may mediate both short and long-term effects on psychosis expression associated with the use of cannabis, possibly through a mechanism of cannabinoid-regulated AKT1/GSK-3signaling downstream of the dopamine D2 receptor. Antipsychotic medications may treat symptoms of psychosis, at least in part, through modulation of the levels and activity of Akt and GSK-3 (Freyberg *et al.* 2010). The Akt pathway appears to play an important role in positive responses to olanzap-

ine. Lu *et al.* (2004) showed that olanzapine stimulates rapid phosphorylation of kinases, such as Akt, which may explain the positive effects of that drug on cell growth and survival. Because previous results have revealed inhibition of Akt signaling in schizophrenia (Beaulieu 2012; Freyberg *et al.* 2010; Keri *et al.* 2011; Park *et al.* 2011), activation of Akt both by drugs and drug-induced increases in insulin level may be another possible explanation of symptom improvement in our patients receiving olanzapine.

One of the major clinical manifestations of hyperinsulinemia and insulin resistance is weight gain. It has been established that antipsychotic drugs are associated with weight gain and other metabolic disturbances such as hyperlipidemia (Dixon *et al.* 2000; Lieberman *et al.* 2005; Smith *et al.* 2011). A growing body of research has demonstrated a link between treatment-emergent weight gain and better therapeutic responses (Czobor *et al.* 2002; Lane *et al.* 2003; Meltzer *et al.* 2003). In study by Procyshyn *et al.* (2007) symptom improvement was independent of weight changes, but was instead related to lipid concentrations. The authors hypothesized that serum lipids can create a physiological depot for neuroleptics (in this particular study-clozapine). Serum lipids can improve the redistribution of the drug into the lipoprotein fraction and the drug's ability to cross the blood-brain barrier (Procyshyn *et al.* 2007). In our study, weight gain was not associated with clinical symptoms, but we cannot exclude the possibility that symptomatic improvement and better therapeutic activity under olanzapine treatment was related to more effective drug redistribution due to changes in serum lipids.

In conclusion, despite the small sample size of this study, we were able to demonstrate that the individual changes in serum insulin levels in the olanzapine-treated patients was inversely correlated with the respective changes in psychopathology profiles, especially in the positive and general symptoms. Our findings suggest that, in addition to insulin levels themselves, the type of the antipsychotic drug administered can be responsible for beneficial effect of insulin on brain function and clinical improvement.

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