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Lithium decreases plasma adiponectin levels in bipolar depression

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HIGHLIGHTS

- At baseline, adipokines levels between BD subjects and controls did not differ.
- Levels of adiponectin significantly decreased after lithium monotherapy.
- Leptin and resistin levels did not change after 6-week lithium treatment.
- Pretreatment levels of leptin were higher in remitters.
- changes in resistin levels were negatively correlated to improvement of depressive symptoms with lithium.

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ABSTRACT

Lithium, a first line treatment for bipolar disorder (BD), has been associated with significant weight gain, but the mechanisms underlying this phenomenon are still unclear. It has been suggested that changes in production/release of adipokines – molecules secreted by adipose tissue presenting anti-inflammatory (adiponectin) and pro-inflammatory (leptin, resistin) properties – might be implicated. Adiponectin, resistin and leptin were assessed in 25 acutely depressed BD individuals (88% medication-free and 68% treatment-naive) at baseline and after 6 weeks of lithium therapy, and in 23 healthy controls matched by age. The 21-item Hamilton Depression Rating Scale was used to assess depression severity. Levels of adiponectin significantly decreased after lithium monotherapy, while the levels of resistin and leptin remained stable after the follow-up period. Adipokine levels during depressive episodes in BD did not differ compared to controls. Pretreatment levels of leptin were higher in remitters and changes in resistin levels were negatively correlated to improvement of depressive symptoms with lithium. Our findings shed light in this pathophysiological process, which might be associated with metabolic syndrome, inflammation and other medical comorbidities in BD.

1. Introduction

Adults with severe mental illness present obesity rates up to 55% [1,2]. Bipolar disorder (BD) has been associated with increased rates of metabolic syndrome presenting with obesity and overweight [2–5]. Patients with BD with obesity present higher recurrence of mood episodes and decreased likelihood of remission [6–12]. Furthermore, overweight/obesity is associated with

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cognitive dysfunction in BD [1,2]. Although lithium is a first-line treatment for BD [2–5], weight gain is a common side effect, experienced by 25–62% of patients using this agent [6–12]. Nevertheless, the mechanisms underlying lithium-induced weight gain remain unclear and have been mostly associated with water retention.

Adipose tissue, traditionally considered only as a source of long-term energy storage, is now investigated on its key role in the integration of systemic metabolism as an endocrine organ due to its property of secreting proteins, collectively referred as adipokines [13,14]. Adipokines may either promote inflammation and metabolic dysfunction or have anti-inflammatory properties, inducing beneficial effects on obesity-linked metabolic disorders [15]. Particularly, leptin, resistin and adiponectin are adipokines known to influence several biological functions involved in the pathophysiology of obesity [15].

Leptin is a pro-inflammatory peptide hormone that regulates food intake and energy expenditure [16]. It acts in a negative feedback loop with the brain by binding to its cognate receptors in the hypothalamus [17]. Leptin levels are elevated in obese subjects probably due to resistance to its action in the central nervous system (CNS) [18]. Rats exposed to chronic unpredictable stress or chronic social defeat stress showed decreased basal levels of leptin in plasma [19]. Also, plasma leptin levels seem to be decreased in MDD regardless of body mass index,[20,21] with similar findings in BD [22] resistin (or "resistance to insulin") interferes on insulin action and has been implicated in several disease processes besides obesity and diabetes, including endothelial dysfunction, thrombosis, angiogenesis, inflammation and smooth muscle cell dysfunction [23,24]. Resistin has also been reported to inhibit dopamine and noradrenaline release in the hypothalamus [25] and has been found to be correlated with atypical MDD symptoms [26].

In addition to the numerous pro-inflammatory adipokines, adipose tissues also express other anti-inflammatory factors, such as adiponectin. Adiponectin is almost exclusively produced by adipocytes and improves insulin sensitivity and fat oxidation [13,27]. Adiponectin deficiency has been linked to metabolic syndrome [28]. Adiponectin expression was found to be decreased in obesity, and studies in experimental animals had shown that adiponectin protects against obesity-related metabolic and cardiovascular disorders [28]. Moreover, adiponectin was also found to be decreased in MDD [26,29,30], while one study reported increased levels among overweight BD patients compared to overweight controls [31].

The objective of this study was to evaluate plasma adipokine levels (resistine, leptin and adiponectin) in BD during a depressive episode and the regulatory effects of lithium treatment on their levels. Adiponectin and leptin have pronounced effects on parameters that regulate weight and enhanced adiponectin levels contributes to weight loss by increasing energy expenditure. We sought to address the following specific questions: (a) does lithium treatment influence the levels of any of these proteins; (b) are the levels of these proteins secreted abnormally at baseline in acutely depressed BD patients; (c) do any of these correlate with baseline levels of depression.

2. Material and methods

Subjects were evaluated between August 2010 and June 2012 at the Institute of Psychiatry, University of Sao Paulo, Brazil. Twenty-five patients, with mean age of 28.5 (±5.7) years were included. The diagnoses of bipolar I (BD-I) ($n = 10$; 40%) or bipolar II disorder (BD-II) ($n = 15$; 60%), current episode depressive, was based on the Structured Clinical Interview for Axis I DSM-IV-TR Disorders (SCID). Other inclusion criteria were: (a) Age between 18 and 45 years; and (b) A score ≥18 in the 21-item Hamilton Depression Scale (HDRS); (c) Less than 3 lifetime major mood episodes; and (d) No more than 5 years of illness duration when enrolled. Exclusion criteria included previous use of lithium (lifetime), rapid cycling in the past 12 months, current Axis I psychiatric disorder other than BD (including substance abuse or dependence), previous history of electroconvulsive therapy, and current significant abnormal laboratory tests or any chronic medical condition. At the onset of study, 22 BD patients (88%) were drug-free for at least 6 weeks and 17 (68%) had never used a mood stabilizer or antipsychotic agent, i.e., were treatment-naive.

At baseline, patients were started on lithium 450 mg/day, and subsequent flexible dosage adjustments were allowed, according to clinical response and serum lithium levels. Plasma lithium levels were obtained at days 7, 14, and at endpoint. Most patients were on lithium monotherapy, although six patients used hypnotic (zolpidem or benzodiazepines) as needed for insomnia.

Patients were age-matched with 23 healthy controls, (10 women; age 27.1 ± 6.6 years). Controls were excluded if they had lifetime history of any axis I psychiatric disorder (by SCID-I), or any first-degree relative with a mental disorder.

The local institutional ethics committee approved the study and all patients provided written consent before the study entry.

2.1. Procedures

Psychometric assessments were made at baseline, on week 1, week 2, week 4, and week 6 (endpoint). Depressive symptoms were measured with the 21-item HDRS. The Young Mania Rating Scale (YMRS) was used to evaluate potential manic switches. All adverse effects were recorded during the follow-up using the *Udvalg for Kliniske Undersøgelser* (UKU) side effects rating scale. Clinical response was defined as a decrease of 50% or more in the Hamilton Depression Rating Scale (HDRS) at endpoint and remission as HDRS <8 at endpoint.

Patients had blood samples collected at baseline and at endpoint (week 6), while healthy controls had only one-point sample collection at baseline. Ten milliliters of blood after 8 h fasting were drawn from each subject by venipuncture into a sodium heparin tube on the same day of the clinical assessment. All procedures were performed between 8 and 10 am to minimize biological differences due to glucocorticoid variation and circadian rhythms. The blood was immediately centrifuged at 3000 *g* for 10 min, 40 C, twice. The plasma was collected and stored at −80 °C until assayed.

Plasma levels of adiponectin, resistin and leptin were measured by enzyme-linked immunosorbent assay (ELISA), according to the procedures supplied by the manufacturer (DuoSet, R&D Systems, Minneapolis, MN, USA). All samples were assayed in duplicate. Detection limits were defined at 5 pg/mL for adiponectin, resistin andleptin. Concentrations are expressed as pg/mL.

2.2. Statistical analysis

Kolmogorov-Smirnov test was used to check if the sample distribution was normal. Between-group comparison of the demographic variables was done using an ANCOVA for continuous variables and the Chi square test for categorical variables. Given that gender distribution differed between groups, within-group comparisons were carried out with repeated measures ANOVA controlling for gender. Correlations between variables were assessed with the Pearson's correlation coefficient. Paired *t*-test was used to investigate changes in adipokines levels before and after treatment. Data are presented as mean ± standard deviation. All tests were two-tailed with a significance level set at 0.05.

3. Results

Demographic and clinical data are summarized in Table 1. The mean lifetime duration of BD was 3.1 ± 1.6 years. BD and control

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Table 1
Sociodemographic and clinical features of the sample.

	Bipolar depression ($n=25$)	Controls ($n=23$)	*P*
Age	28.5 ± 5.7	27.1 ± 6.6	0.45
Gender (female/male)	19/6	10/13	0.02
Body mass index (kg/m^2)	29.0 ± 6.0	25.7 ± 4.3	0.13
Use tobacco currently (yes/no)	7/18	6/17	0.57
Illness duration (years)	3.1 ± 1.6		

subjects did not significantly differ in age, body mass index and current tobacco use. Mean serum lithium level at endpoint was 0.49 ± 0.16 mEq/L. Out of the 25 BD patients evaluated, 21(84%) presented clinical response and 14(64%) achieved remission criteria at week 6.

Overall, baseline levels of adiponectin, leptin, and resistin were similar between patients and controls (Fig. 1a–c). There was no difference in BMI between remitted BD subjects and controls. Adiponectin, resistin or leptin levels did not differ between BD subjects and healthy controls at baseline after controlling for gender.

Pre and post lithium adipokine's levels differed only for adiponectin. The mean level of adiponectin decreased from 10153 ± 1668 pg/mL pretreatment to 8897 ± 2511 pg/mL post treatment ($t=2.13$ $p<.05$) (Fig. 1a). No significant differences (ns) on adiponectin, leptin or resistin levels at endpoint were observed between BD patients with low (0.2–0.5 mEq/L) vs. high (>0.5 mEq/L) blood lithium levels. Also, BD patients who reported weight gain during the follow-up ($n=7$) showed similar levels (ns) of post treatment adiponectin, leptin and resistin relative to BD subjects who did not notice weight gain.

Baseline levels of adiponectin or resistin did not predict remission (ns). Nevertheless, pretreatment levels of leptin were higher in remitters (2351 ± 353) vs. non-remitters (2220 ± 804 pg/mL; $p<.01$) BD patients. Changes in resistin levels were negatively correlated to the over time reduction in HDRS scores ($p<.05$; $r=-0.40$).

4. Discussion

This is the first study to investigate changes on adipokine levels during lithium treatment in BD. It is described for the first time a significant reduction on adiponectin levels after 6 weeks of lithium treatment in bipolar depression. However, no difference on any adipokine was observed in BD depression relative to controls at baseline. Finally, only resistin showed a significant association with depressive symptoms. Most studies reported a decrease in peripheral adiponectin levels in MDD [26,29,30], while in BD the only study available to date reported increased levels in overweight subjects [31]. Lower adiponectin levels in MDD have been associated with increased depression severity [30] and with atypical depressive symptoms [26].

To the best of our knowledge only one study investigated adipokines in BD. That was a cross sectional study with thirty overweight subjects with BD in euthymia (using multiple medications) and 30 controls were evaluated in a cross sectional study. It was described an increase in adiponectin and leptin levels [31]. Our study was the first to quantify adipokines in symptomatic BD patients and no difference was observed in acutely depressed BD patients compared to healthy controls. On the other hand, it has to be noted that our sample was not overweight at baseline and we lack information on BMI at endpoint. Using the side effects scale (UKU), it was shown that 28% of the BD patients reported weight gain during the 6 weeks of lithium treatment. Nonetheless, BD patients reporting weight gain during the follow-up exhibited similar post treatment levels adiponectin (as well as resistin and leptin) relative to those patients who did not notice weight gain. Although this result does not support the hypothesis that lithium-induced decreases in adiponectin might relate to the potential of lithium to produce weight and metabolic changes, the short-term nature of our study (6 weeks) precludes any definitive conclusion in this regard.

Our results showed adiponectin levels decreasing after lithium treatment in bipolar depression. For the first time, lithium effect on adiponectin is reported in humans. Lower adiponectin levels have been reported in metabolic syndrome, characterized by obesity, insulin resistance, impaired glucose tolerance, hyperlipidemia and cardiovascular morbidity [28]; comorbidities that are also associated with lithium treatment [6,8,10,12].

Limitations of this study are the absence of weight information at endpoint and the fact that BD and healthy controls had a gender mismatch distribution.

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5. Conclusion

Decreasing levels of adiponectin during lithium treatment might be associated with lithium-induced weight gain, metabolic syndrome and cardiovascular comorbidities. Long-term follow-up studies are necessary to confirm the association between early changes in adiponectin levels and weight gain during the course of treatment in BD.

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