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Short Communication

Leptin serum concentrations are associated with weight gain during lithium augmentation

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ABSTRACT

Background: Meta-analytical data show lithium augmentation (LA) as an effective treatment strategy in major depression. Weight-gain is a common side effect of LA. The proteohormone leptin is discussed to be involved in the pathophysiology of weight gain induced by psychopharmacological treatment. The purpose of our study was to investigate the association of leptin and body mass index (BMI) during LA in a prospective cohort study.
Methods: Leptin serum concentrations and body mass index (BMI) were measured in a total of 89 acute depressive patients before and then after four weeks of LA.
Results: In a linear mixed model analysis the following variables had a significant positive effect on BMI: time (equal with "treatment effect of LA"; $F_{1.83} = 6.05$; $p = 0.016$) and leptin ($F_{1.111} = 13.83$; $p = 0.0003$) as well as the covariates male gender ($F_{1.89} = 5.08$; $p = 0.027$) and adiposity ($F_{1.85} = 105.13$; $p<0.0001$).
Limitations: If the reported effect of leptin on BMI is specific to LA remains unclear without a control group.
Conclusion: Leptin signalling might be involved in lithium-induced weight-gain.

1. Introduction

In case of nonresponse to antidepressant-treatment the add-on treatment with lithium – the so-called lihium augmentation (LA) – is an effective strategy in the treatment of major depressive disorder (MDD). Weight gain is a common side effect of lithium treatment – it can lead to obesity, metabolic diseases and it is a significant reason for treatment discontinuation and decreased life quality. The underlying mechanism of lithium induced weight gain is incompletely understood.

Leptin, a pro-inflammatory, anorexigenic peptide hormone, is primarily secreted by the white adipose tissue. Binding to its hypothalamic receptor, leptin seems to influence several biological functions involved in the pathophysiology of obesity: it decreases body weight both by suppressing appetite and by increasing energy expenditure. Leptin levels are elevated in obese subjects and several lines of evidence show that leptin receptor resistance plays a key role in the pathophysiology of adiposity (Maffei et al., 1995; Lu, 2007).

Weight gain during treatment with psychiatric drugs is discussed to be associated with an increase in leptin levels. Therefore leptin and leptin receptor resistance, respectively, could play an important role in weight gain induced by psychiatric pharmacotherapy. There are several studies investigating leptin levels and weight under treatment with atypical antipsychotics (Potvin et al.,

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2015) and antidepressants (e.g. Schilling et al., 2013), whereas data for lithium-treatment are limited.

The purpose of our study was to investigate the association of leptin on body mass index (BMI) during LA in a prospective cohort study. To our best knowledge this is the first study investigating leptin levels and BMI during LA. We assumed that BMI during LA is associated with leptin serum levels.

2. Methods

2.1. Patients:

The study population consists of a subsample of a prospective cohort study investigating treatment response and side effect burden of LA in MDD. In this subsample data on serum levels and BMI (kg/m^2) were available in 89 patients. Inclusion criteria were: MDD, age older than 18 years, indication for an antidepressant pharmacotherapy, insufficient response to an adequate antidepressant pre-treatment and clinical indication for LA, Hamilton Depression Rating Scale (HDRS-17; Hamilton 1960) score ≥12 and written informed consent. Diagnosis was confirmed by the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998). Patients were recruited between December 2008 and December 2012 in 12 psychiatric departments of the Berlin Research Network on Depression, Berlin, Germany. The majority of patients were inpatients (15 ambulants and 74 inpatients). Local ethics committees approved the study, and written informed consent was obtained from all subjects.

2.2. Procedures:

In this longitudinal study leptin serum concentrations (non-fasting) were measured first in medicated patients before LA (baseline) and then after four weeks of LA (endpoint). Severity of depression (measured with HDRS-17) and BMI were measured on both occasions. Adiposity was defined as a BMI ≥ 30. Blood samples were collected by peripheral venepuncture (10 ml drawn into a sodium-heparin tube). Blood was centrifuged at 3000 g for 10 min, 40C, twice. Serum was collected and stored at −80C until assayed. All patients received individual doses of lithium carbonate adapted to their individual lithium serum levels and one or more antidepressants (see Table 1).

2.3. Laboratory analysis

Endogenous leptin-levels (pg/ml) were measured in the re-thawed serum samples using the RayBio® Human Leptin ELISA kit, an in vitro enzyme-linked immunosorbent assay for the quantitative measurement of human leptin, according to the manufacturer's instructions. The minimum detectable dose of human leptin was determined to be 2 pg/ml.

2.4. Statistical analysis:

We used a linear mixed model for statistical analysis to investigate the effect of LA (time) and leptin levels as well as potentially confounding covariates as explanatory factors for change in BMI (dependent variable). Linear mixed-effects models have the advantage of allowing the investigation of variability between patients (heterogeneity) and simultaneously adjusting for the within-subject correlation. In the present analysis, random effects were permitted for the intercepts. We entered time, leptin levels, age, gender, lithium serum level at endpoint, HRDS-17 score, psychopharmacological co-medication with a high risk of weight-gain and adiposity at baseline as fixed effects into the

Table 1
Clinical data and results.

	n (%)				
Patients	89 (100)				
Female	53 (59,6)				
Male	36 (40,4)				
Adiposity at baseline	15 (16.9)				
Psychotropic co-medication[1]					
Antidepressants					
SSRI	50 (56.2)				
SNRI	25 (28.1)				
TCA	8 (9.0)				
NDRI	4 (4.5)				
Agomelatin	2 (2.2)				
NaSSA	11 (12.4)				
MAO-I	2 (2.2)				
Second generation antipsychotics	25 (28.2)				
Antiepileptic drugs	7 (7.9)				
Benzodiazepines	20 (22.5)				
Low-potency antipsychotics	4 (4.5)				
		Mean (SD)	**n (%)**	**Mean (SD)**	
Age (years)	89 (100)	49.55 ± 15.41			
Lithium serum level (mmol/ml) at last visit[2]	80 (89.9)	0.715 ± 0.15			
		Before lithium augmentation		**After lithium augmentation**	**p-value**[*]
Leptin serum level (in pg/ml)[2]	89 (100)	265,78 ± 366,79	89 (100)	304,73 ± 463,63	p < 0.05[***]
logarithmised (common logarithm) leptin serum level (in pg/ml)	89 (100)	2.16 ± 0.52	89 (100)	2.21 ± 0.56	p = 0.065[**]
HRDS-17 score	88 (98.9)	21.45 ± 4.93	89(100)	12.19 ± 7.08	p < 0.05[**]
BMI (kg/m^2)	89 (100)	25.55 ± 5.67	87(97.8)	25,91 ± 5.63	p < 0.05[**]

[*] Significance level was set at 0.05 in all analyses (two-sided); [**] paired sample *t*-test; [***] non parametric Wilcoxon test; [****] spearman correlation.
SSRI = Serotonin Reuptake Inhibitors; SNRI = Serotonin and Norepinephrine Reuptake Inhibitor; TCA: Tricyclic Antidepressant; NDRI = Norepinephrine and Dopamine Reuptake Inhibitor (Bupropione); Reuptake Inhibitor; NaSSA = Noradrenergic and specifically serotonergic Antidepressant (Mirtazapine); MAO-I = Mono Amine Oxidase Inhibitor (Tranylcypromine); SD = standard deviation; HDRS-17 = Hamilton Depression Rating Scale; BMI = body mass index.

[1] Antidepressant, antipsychotic and antiepileptic pre-medication was maintained during lithium augmentation (LA) except in four patients: one patient was switched from pre-treatment with "bupropione plus escitalopram " to "venlafaxine" after two weeks; in one patient olanzapine (week two to week four) and quetiapine (week four until endpoint) was added; in one patient risperidone (minor dose of 0.25mg/day, week 3 until endpoint) was added; in one patient agomelatine and trimipramine (minor dose of 25mg/day) was added (week two until endpoint).

[2] No significant correlation was found between leptin- and lithium-erum levels after four weeks of LA (Spearman-correlation; p > 0.05).