European Psychiatry 35 (2016) 1–7

Contents lists available at ScienceDirect

European Psychiatry

journal homepage: http://www.europsy-journal.com

Review

Leptin in bipolar disorder: A systematic review and meta-analysis

B.S. Fernandes [a,b,*], S. Dash [a], F. Jacka [a], S. Dodd [a,f], A.F. Carvalho [c], C.A. Köhler [c], J. Steiner [d], M. da Graça Cantarelli [b], P. Nardin [b], C.-A. Gonçalves [b], M. Berk [a,e]

[a] Deakin University, IMPACT Strategic Research Centre, School of Medicine, and Barwon Health, Geelong, Australia
[b] Laboratory of Calcium Binding Proteins in the Central Nervous System, Department of Biochemistry, Federal University of Rio Grande do Sul, Porto Alegre, Brazil
[c] Translational Psychiatry Research Group and Department of Clinical Medicine, Faculty of Medicine, Federal University of Ceará, Fortaleza, CE, Brazil
[d] Department of Psychiatry, University of Magdeburg, Magdeburg, Germany
[e] Florey Institute for Neuroscience and Mental Health, Department of Psychiatry and Orygen, The National Centre of Excellence in Youth Mental Health, University of Melbourne, Parkville, Australia
[f] Department of Psychiatry, University of Melbourne, Parkville, Australia

ARTICLE INFO

Article history:
Received 30 December 2015
Received in revised form 20 February 2016
Accepted 21 February 2016
Available online 8 April 2016

Keywords:
Biomarker
Leptin
Bipolar disorder
Mania
Depression
Meta-analysis

ABSTRACT

Background: Bipolar disorder (BD) is a psychiatric disorder associated with increased rates of obesity and inflammation. Leptin is an adipokine that is mainly produced by the white adipose tissue in response to insulin. It stimulates the immune system, increasing the production of pro-inflammatory cytokines. There is currently uncertainty regarding possible alterations in peripheral leptin levels across the mood states in BD.

Methods: This study comprises a between-group meta-analysis comparing serum and plasma leptin levels in people with BD in mania, depression or euthymia and healthy controls. We conducted a systematic search for all possibly eligible-English and non-English peer-reviewed articles. We calculated the effect size (ES) utilizing Hedges' adjusted g using random effects.

Results: Eleven studies were included in the meta-analyses, providing data on 1118 participants. Serum and plasma leptin levels were not altered in subjects with BD when compared to healthy controls in mania ($g = -0.99$, 95% CI −2.43 to 0.43, $P = 0.171$), in depression ($g = 0.17$, 95% CI −0.45 to 0.79, $P = 0.584$), or in euthymia ($g = 0.03$, 95% CI −0.39 to 0.46, $P = 0.882$). However, we did observe a stronger association between leptin levels and both age and BMI in patients with BD in euthymia compared to healthy controls, such that the greater the age of the individuals, the greater the difference in leptin levels between BD and controls; and the higher the BMI, the greater the difference in leptin levels between BD and controls.

Conclusions: Our meta-analysis provides evidence that leptin levels are not altered in BD across the mood spectrum compared to healthy controls. The disproportionate increase of leptin levels with increase in BMI in BD speaks in favour of a potential inflammatory role of white adipose tissue in BD and a disproportionate increase of leptin levels with increase in age.

1. Introduction

Bipolar disorder (BD) is one of the psychiatric disorders with the most severe burden of illness [1]. This is not just because of its effects on mood and cognition, but also due to its increased clinical morbidity; BD is associated with increased odds for atherosclerosis and cardiovascular disease [2]. This is thought to be mediated, at least partially, by high rates of obesity and metabolic syndrome – nearly twice the rates of the general population [3].

Obesity is associated with a chronic state of low-grade inflammation, presenting increased levels of markers of inflammation, such as insulin, C-reactive protein (CRP), and pro-inflammatory cytokines [4]. Psychiatric disorders, including BD, are characterized by a similar pattern of low-grade inflammation, with insulin, CRP and inflammatory cytokines levels, such as interleukin 6 (IL6) and tumour necrosis factor alpha (TNFα), abnormally increased, even during euthymia [5–8]. This suggests that BD and obesity, at least to some degree, might share the same biological underpinnings.

* Corresponding author at: Deakin University, School of Medicine, Barwon Health, Geelong, Victoria, Australia.
E-mail address: brisasf@gmail.com (B.S. Fernandes).

http://dx.doi.org/10.1016/j.eurpsy.2016.02.003
0924-9338/

Leptin is an adipokine produced by the white adipose tissue mainly in response to insulin. It stimulates the immune response, increasing the production of IL6 and TNFα, and it also modulates insulin sensitivity, with higher levels of leptin promoting insulin resistance and perpetuating a positive feedback loop. Leptin, which is produced in the periphery by adipocytes, crosses the blood–brain barrier (BBB) in a unidirectional fashion; in the brain, it directly regulates energy homeostasis and has been implicated in mood disorders [9]. Accordingly, the "selfish brain theory" postulates that impaired cerebral glucose utilization leads to secondary peripheral metabolic changes and consequent pro-inflammatory changes and increased cardiovascular risk [10].

Several studies have been conducted assessing leptin levels in the peripheral blood of people with BD, with conflicting results. In mania and depression, some studies show that leptin levels are decreased, some are increased, and some show no difference when compared to healthy controls. In euthymia, the same pattern of equivocal findings is evident [11–21].

Heterogeneous patient populations, variations in methodology or small sample sizes lacking statistical power might cause these inconsistent findings. Meta-analysis is a recognized technique used to resolve discrepancies between studies. It is a quantitative method that combines results from independent studies to increase statistical power in order to derive more solid conclusions [22]. This allows one to distinguish small or inconsistent effects from no effect. It also helps to determine whether the variation in effects between studies is merely due to the expected random statistical fluctuation, or instead to sample variations, trait assessment or publication bias. In addition, the technique of meta-regression may be used to evaluate confounders and discrepancies among different studies [23].

The aims of this study were thus to verify if peripheral leptin levels are altered in BD and if there are differences among mood states concerning this inflammatory marker. With this in mind, we performed a meta-analysis of all cross-sectional studies that compared serum and plasma leptin levels between patients with BD and healthy subjects in order to clarify the role of leptin as a potential underpinning mechanism and as a biomarker involved in BD.

2. Methods and materials

This study comprised a between-group meta-analysis comparing serum and plasma leptin levels in people with BD in mania, depression or euthymia, and in healthy controls. We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA Statement) and the Cochrane Collaboration [23]. The literature search, decisions on inclusion, data extraction and quality control were all performed independently by two of the authors (BSF and CAG).

2.1. Search strategy

We conducted a systematic search for all possibly eligible-English and non-English peer-reviewed articles to avoid language publication bias [24,25] using Medline, Embase, the Cochrane Library, Scielo, PsycINFO, Scopus, and Web of Knowledge. No year or country restrictions were used. The search term used for the electronic database search was (leptin) AND (bipolar OR psychosis OR mania OR manic OR depressed OR depression). The last search was performed in September 2015. We then manually checked the reference sections of the publications found through our electronic search to identify additional studies that may have been missed. Study selection eligibility and exclusion criteria were pre-specified.

2.2. Study selection

Inclusion criteria were as follows: (1) adult subjects with BD in manic, depressive, or euthymic states, as defined by DSM-IV-TR (American Psychiatric Association, APA); (2) pairwise comparison to a control group of healthy volunteers; (3) studies assessing circulating serum or plasma leptin in human blood samples in vivo. Exclusion criteria were as follows: (1) duplicate reports and (2) lack of a control group. The decision on whether to include studies in the meta-analysis was made based on the above criteria, and a consensus was reached among the authors on those decisions.

2.3. Data extraction

To avoid potential errors, two reviewers (BSF and CAG) independently extracted data [*n*, mean and standard deviation (SD)]. We extracted the following data: diagnostic status, leptin levels, sex, age, body-mass index (BMI), medication, Young Mania Rating Scale (YMRS) and Hamilton Depression Rating Scale (HDRS) scores. Using the information available from these studies, we performed the analyses according to mood state (i.e., mania, depression, or euthymia). Subjects with BD were considered drug-free if they were off psychiatric medication for at least two weeks prior to blood withdrawal. Discrepancies in data entry were double-checked by the reviewers with the original published data, and consensus was reached. When the necessary data were not available from the published papers, we contacted the authors and requested the necessary information. If the results were graphically presented and the authors could not provide the data, we used a method for data extraction from the graphs explained by Sistrom et al. [26]. Whenever multiple reports pertained to the same groups of patients, we retained only the most comprehensive report for the meta-analytic calculations to avoid duplication of information [23]. In the case of longitudinal studies, which also had a control group, we used data from both time points compared to controls.

2.4. Publication bias

Studies with negative results are less likely to be published than studies with positive results. To account for significant publication bias, we analyzed a funnel plot graph, a scatter plot of the effect size against a measure of study size, and the Egger test [27]. In addition, the Orwin's fail-safe N test (file drawer statistic) was used to quantify the number of possible negative omitted studies that would be required to make potentially significant results non-significant ($P > 0.05$) [28]. The trim-and-fill procedure, which is a validated model to estimate an effect size (ES) after bias has been taken into account, was employed when the funnel plot was symmetrical to further verify possible effects of publication bias.

2.5. Statistical analysis

Comprehensive Meta-analysis Software (CMA) version 2.0 was employed in all analyses. Because studies used different measurement methods, standardized mean difference estimates of the differences in leptin levels between subjects with BD and healthy controls were used as the effect size (ES), utilizing Hedges' adjusted *g*. This provides an unbiased ES adjusted for small sample sizes. The 95% confidence interval (95% CI) of the ES was also computed [22,29]. An ES of 0.2 is considered as indicating a low effect, meaning a small difference in leptin levels between subjects with BD and controls, 0.5 a moderate effect, and 0.8 a large effect.

We assessed the heterogeneity across studies using the Cochran *Q* test, a weighted sum of the squares of the deviations of individual study ES estimates from the overall estimate, and a *P*-value of