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Review article

Leptin and adiponectin levels in major depressive disorder: A systematic review and meta-analysis

Bing Cao[a,b], Yan Chen[b], Elisa Brietzke[b,c], Danielle Cha[b,d], Aisha Shaukat[b], Zihang Pan[b], Caroline Park[b], Mehala Subramaniapillai[b], Hannah Zuckerman[b], Kiran Grant[b], Rodrigo B. Mansur[b], Roger S. McIntyre[b,e,f,g,*]

[a] Department of Laboratorial Science and Technology, School of Public Health, Peking University, Beijing 100191, PR China
[b] Mood Disorders Psychopharmacology Unit, University Health Network, Toronto, Canada
[c] Department of Psychiatry, Universidade Federal de São Paulo, São Paulo, Brazil
[d] Faculty of Medicine, School of Medicine, University of Queensland, Brisbane, QLD, Australia
[e] Department of Psychiatry, University of Toronto, Toronto, Canada
[f] Department of Pharmacology, University of Toronto, Toronto, Canada
[g] Brain and Cognition Discovery Foundation, Toronto, ON, Canada

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ABSTRACT

Objectives: To explore differences in adipokine levels (i.e., leptin and adiponectin levels) between adults with Major Depressive Disorder (MDD) and healthy controls (HC), and to discuss the possible role of adipokine regulation in the development and progression of MDD.

Methods: A systematic review and meta-analysis were conducted based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. A systematic search was conducted for all English and Chinese peer-reviewed articles from inception to November 2017. A random effects model was used to calculate the standardized mean difference (SMD) of leptin and/or adiponectin levels in subjects diagnosed with MDD versus HC within a 95% confidence interval (CI).

Results: Thirty-three studies were included in this meta-analysis. In total, 4,372 (52.3%) subjects with MDD and 3,984 (47.7%) HC were compared. We identified significant lower adiponectin levels in MDD compared to HC with a small effect size (ES) (SMD = −0.25; 95% CI: −0.48, −0.02; $P < 0.001$). However, no significant difference was observed in leptin levels between MDD subjects and HC (SMD = 0.13; 95% CI: −0.06, 0.31; $P = 0.170$). The heterogeneity in the results of our meta-analysis could not be completely explained by dividing subjects into subgroups. Results from subgroup analyses suggested that studies involving samples with BMI ≥ 25 had lower adiponectin levels in subjects with MDD compared to HC, and older age samples (i.e., age ≥ 40) with BMI ≥ 25 had both higher leptin levels and lower adiponectin levels in MDD subjects as compared to HC.

Limitations: The heterogeneity of included studies, small sample sizes, and potential publication bias were significant limitations.

Conclusions: The current systematic review and meta-analysis indicated that lower adiponectin levels may be associated with MDD. Moreover, the results suggest that males expressing lower adiponectin and leptin levels have an increased likelihood of developing MDD. Future studies should aim to investigate the manifestation of depressive phenotypes in older, obese populations with altered metabolic profiles resulting from adipokine dysregulation.

The review has been registered with PROSPERO (registration number CRD42018082733).

1. Introduction

Major Depressive Disorder (MDD) is one of the leading causes of global burden of disease (Hung et al., 2007), with an increased prevalence of approximately two-fold in women compared to men (Kessler, 2003). One of the main challenges of treating individuals with MDD is the presence of comorbidities, especially Metabolic Syndrome (MetS) (i.e., abdominal obesity, high blood pressure, elevated blood glucose, high serum triglycerides, and low/high-density lipoprotein levels), Type II Diabetes Mellitus (T2DM), and excessive weight/obesity

* Corresponding author at: Mood Disorders Psychopharmacology Unit, University Health Network, Toronto, Canada.
E-mail address: roger.mcIntyre@uhn.ca (R.S. McIntyre).

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(Iosifescu et al., 2003; Liu et al., 2013; McIntyre et al., 2017; McIntyre et al., 2012). Notably, subjects with MDD are more susceptible to be disproportionately affected by alterations in the metabolic milieu [i.e., abnormal adipokine profile such as higher/lower pro-inflammatory cytokine level compared to healthy controls (HC), neurotransmitter dysregulation, abnormal release/reuptake of neurotransmitters]. These observations have been well demonstrated to affect an individual's illness trajectory, progression, and treatment response (Cha et al., 2016; Mansur et al., 2017a; Mansur et al., 2017b; Yamagata et al., 2017).

Adipose tissue has recently been proposed as an important mediator in the onset and progression of MDD, as well as a critical determinant of treatment response and remission (Hawkins et al., 2015; Jantaratnotai et al., 2017; Sanderlin et al., 2017a, b; Tulloch et al., 2017). Specifically, there is evidence indicating that the production of adipokines (i.e., adiponectin, leptin) by adipose tissues in response to an increase in total fat mass, has effects on the brain. These adipokines serve as neuropeptide messengers that act on receptors in the hypothalamus to alter feeding behavior (e.g. increasing food intake and decreasing energy expenditure) (Leo et al., 2006; Tuncel et al., 2016). Moreover, both leptin and adiponectin have been implicated in inflammatory processes (Shariq et al., 2018), such as an increased release of pro-inflammatory cytokines, interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha) (Leo et al., 2006; Yang et al., 2007), altered energy balance due to nutritional overload, and an increase in weight/obesity as a consequence of leptin resistance and oxidative stress (Kurt et al., 2007; Yang et al., 2007; Zeman et al., 2009). Oxidative stress results from an imbalance between the production of reactive oxygen species (ROS) and the ability of a biological system to detoxify the ROS and/or repair the resulting damage. ROS result from reactions involving free radicals, which are generated during consumption of glucose into ATP, CO_2, electrons in aerobic mitochondria (Liemburg-Apers et al., 2015).

Sex differences in the concentration of adiponectin and leptin have been reported, with there being a higher serum concentration in women than in men (Arita et al., 2012; Considine et al., 1996; Rosenbaum et al., 1996; Tchernof and Despres, 2013). In addition, there is evidence to suggest that there are sex differences in the association between leptin and/or adiponectin concentration with insulin resistance (Al-Daghri et al., 2011; Matsuda et al., 2005), androgen level (Bottner et al., 2004), and MetS (Eglit et al., 2013).

Alterations in the level of leptin and adiponectin in individuals with MDD, insulin resistance, obesity, and/or systemic inflammation offer an opportunity to investigate leptin and adiponectin as potential biomarkers in the development and progression of mood and metabolic disorders (Gil-Campos et al., 2004; Soczynska et al., 2011; Taylor and Macqueen, 2010). The fact that as most patients with MDD fail to fully recover in terms of cognition, workplace function and measures, or motivation and reward (Huang, 2009; Ragguett et al., 2016) with existing treatments, suggests other potential mechanism and treatment targets should be explored. To our knowledge, two meta-analyses were previously published by Carvalho et al. 2014 and Hu et al. 2015. Our study reported updated research results, and also explored more details about the role of different variables in the leptin and adiponectin levels in MDD. In addition, we included the more recent research results and also considered the relationship of sex and adiponectin/ leptin levels. Therefore, the objectives of this systematic review and meta-analysis are to (1) examine the relationship between levels of different adipokines (i.e., leptin and adiponectin) in MDD compared to HC, and (2) explore the mechanistic role of leptin and adiponectin in the pathogenesis of MDD, taking into consideration sex-related differences.

2. Methods

2.1. Literature search

Following the *preferred items for reporting of systematic reviews and meta-analyses* (PRISMA) guidelines (Moher et al., 2009), a systematic literature search from inception to November 2017 was performed to identify studies reporting on leptin and/or adiponectin levels in blood samples (i.e., serum, or plasma) in individuals with MDD. Included articles were indexed in the following databases: Cochrane Library, PsycINFO, PubMed/Medline, EMBASE, Web of Science. In addition, the China National Knowledge Infrastructure (CNKI) and VIP information (VIP) were used to search for articles published in Asia. Search terms included “Major Depressive Disorder OR depression OR depressive”, “leptin”, “adiponectin”, “adipokines”.

2.2. Identification of eligible studies

Studies were included based on the following criteria: (1) the study reported on outcomes in a human population; (2) the study used a cross-sectional, case-control, or cohort design; (3) the study included a control group of subjects with no personal or family history of mental illnesses; (4) the study included a group of depressed subjects who met the *diagnostic and statistical manual of mental disorders* (DSM) or *international classification of diseases and related health problems* (ICD) criteria for MDD; (5) the researchers measured leptin and/or adiponectin levels in all subjects; and (6) the leptin and/or adiponectin levels in case and control groups were available for analysis.

Studies were excluded based on the following criteria: (1) the leptin or adiponectin levels were not evaluated in association with depressive symptoms and/or disorders; (2) the study did not include a control group; (3) the study was a duplicate publication using the same dataset by the same or different authors (i.e., only the most recent reports were included); (4) the study did not contain explicit measures of leptin and adiponectin for each group. Data were extracted from all studies meeting the foregoing inclusion and exclusion criteria.

2.3. Data extraction and quality assessment

Two investigators abstracted information independently for each eligible article using a standardized form. The following information was extracted from each study: first author, publication year, study design, country, geographic location, age, sex (i.e., female, male), body mass index (BMI), type of blood sample specimen required for test (i.e., plasma, serum), sample detection method (i.e., ELISA, RIA, or other), depression subtype, sample size, subjects’ mean leptin and/or adiponectin levels, and standard deviation (SD). The data was extracted if subjects were divided into subgroups according to sex, including the number of subjects in the MDD and HC groups, and the number of participants in the male and female subgroups. The mean and SD of leptin/adiponectin levels were calculated for each subgroup. Additional subgroups were created based on living standards, geographic region, study method, age, and BMI. Studies were divided into two groups according to their publication date. To create subgroups based on living standards, studies were divided into two groups according to their publication date (i.e., before 2010 versus after 2010). This operationalization is supported by evidence demonstrating a significant difference in living standards before 2010 compared to after 2010 (Liu et al., 2016). Studies were divided into Asian/European/North American subgroups based on the geographic location of where studies were completed. Due to the heterogeneity of study methods, subgroups were also created based on differences in sample (i.e., plasma or serum) and detection methods (i.e., ELISA, RIA, or other). Subjects were also divided into subgroups based on age (i.e., age < 40 and age ≥ 40), given the association between age and metabolic status (Fishbane et al., 2012). Finally, since the secretion of adiponectin and leptin from fat cells has been shown to increase proportionally with total fat mass., subjects were divided into two subgroups according to BMI (i.e., BMI < 25 and BMI ≥ 25 subgroups) (Iwan-Zietek et al., 2016).

The Newcastle–Ottawa scale (NOS) is a risk of bias assessment tool for observational studies, and is recommended by the Cochrane collaboration (Lo et al., 2014). NOS was applied to assess the quality of the