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Shared metabolic and immune-inflammatory, oxidative and nitrosative stress pathways in the metabolic syndrome and mood disorders

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ABSTRACT

This review examines the shared immune-inflammatory, oxidative and nitrosative stress (IO & NS) and metabolic pathways underpinning metabolic syndrome (MetS), bipolar disorder (BD) and major depressive disorder (MDD). Shared pathways in both MetS and mood disorders are low grade inflammation, including increased levels of pro-inflammatory cytokines and acute phase proteins, increased lipid peroxidation with formation of malondialdehyde and oxidized low density lipoprotein cholesterol (LDL-c), hypernitrosylation, lowered levels of antioxidants, most importantly zinc and paraoxonase (PON1), increased bacterial translocation (leaky gut), increased atherogenic index of plasma and Castelli risk indices; and reduced levels of high-density lipoprotein (HDL-c) cholesterol. Insulin resistance is probably not a major factor associated with mood disorders. Given the high levels of IO & NS and metabolic dysregulation in BD and MDD and the high comorbidity with the atherogenic components of the MetS, mood disorders should be viewed as systemic neuro-IO & NS-metabolic disorders. The IO & NS-metabolic biomarkers may have prognostic value and may contribute to the development of novel treatments targeting neuro-immune, neuro-oxidative and neuro-nitrosative pathways.

1. Introduction

Mood disorders, including major depressive disorder (MDD) and bipolar disorder (BD), are among the leading causes of disability worldwide (Walker et al., 2015). Recent meta-analyses indicate that the prevalence of metabolic syndrome (MetS) is substantially higher among individuals with MDD and BD (Vancampfort et al., 2015). In addition, several lines of evidence indicate that MDD and BD may predispose individuals, even at an early age, to accelerated atherosclerosis and cardiovascular disease (CVD) and MetS (Goldstein et al., 2015). MetS comprises a set of changes that increase the risk for hypertension, type 2 diabetes mellitus (T2DM), diabesity (late-life diabetes associated with obesity) and CVD (Lakka et al., 2002). MDD and BD are highly comorbid with CVD, T2DM, obesity, dyslipidemia and insulin resistance (Benton et al., 2007; Kupfer, 2005; Leboyer et al., 2012; Murphy et al., 1987). Individuals with MetS are more likely to present depressive symptoms than those without (Capuron et al., 2008). MetS comorbidity in mood disorders is associated with a more complex affective presentation, lower probability of recovery, and more frequent episodes and suicide attempts (Fagiolini et al., 2005; Fries et al., 2012; Grande et al., 2012; McIntyre et al., 2012a; Thomas et al., 2008).

Multiple interacting pathways contribute to the comorbidity between mood disorders (MDD and BD) and MetS or cardiovascular disease, including immune-inflammatory alterations; disturbances in

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the regulation of oxidative and nitrosative stress as well as mitochondrial dysfunction (Anderson and Maes, 2015a,b; Maes, 2009; Moylan et al., 2014; Pena et al., 2014). Moreover, the same pathways may prime patients with mood disorders to developed metabolic disorders, including disorders in lipid metabolism and increased atherogenicity (Maes et al., 2011d).

The infiltration of adipose tissue by macrophages may have a significant role in the pathophysiology of low-grade inflammation in MetS (Moreno-Indias et al., 2016) as supported by animal and human studies (Shi et al., 2016). In addition, higher peripheral levels of C-reactive protein (CRP) and other inflammatory factors appear to be risk factors for the development of MDD and BD (Capuron et al., 2008; Dixon et al., 2008; Maes et al., 1995; Valkanova et al., 2013; Wium-Andersen et al., 2016). Activation of pro-inflammatory cytokine networks can induce affective symptoms by interacting with and modulating many pathophysiological domains that are altered in MDD and BD, including the patterning and levels of different neurotransmitters; alterations in metabolism; changes in neuroendocrine functions; changes in synaptic plasticity; decreased neurogenesis; and increased hypothalamic-pituitary-adrenal (HPA) axis activation (Anderson and Maes, 2015a,b; Leonard and Maes, 2012; Morris and Berk, 2015). The wider medical comorbidities associated with MDD and BD, including CVD, neuroinflammatory/neurodegenerative and (auto) immune disorders, are also associated with many of these pathophysiological alterations, including increased activated immune-inflammatory pathways, as well as alterations in the IO & NS pathways (Bortolato et al., 2016a,b; Goldstein et al., 2009; Jiang et al., 2014; Maes et al., 2011d; Maes et al., 1995).

The mechanisms underlying the associations between MetS and mood disorders may also be linked to insulin resistance, which is associated with alterations in insulin-like growth factor, immune and oxidative pathways and glucocorticoids (Belvederi Murri et al., 2016; Goldsmith et al., 2016; McIntyre et al., 2010; Stetler and Miller, 2011; Tu et al., 2016). Furthermore, a putative 'metabolic-mood syndrome' has been recently conceptualized (Mansur et al., 2015; Vogelzangs et al., 2011). According to this theoretical framework, individuals with mood disorders and co-morbid obesity may express distinctive pathophysiological mechanisms and a more severe cognitive dysfunction (Liu et al., 2013, 2014; McElroy and Keck, 2014; McIntyre et al., 2010). The etiology of MetS is multifactorial and includes an unhealthy lifestyle, which can be exacerbated by psychiatric symptoms, adverse effects of pharmacological treatments (e.g., certain atypical antipsychotics), and limited access to health care (McIntyre et al., 2012b; Vancampfort et al., 2013b).

The purpose of this study is to delineate the pathophysiological role of shared IO & NS and metabolic pathways and their interconnections in the reciprocal association between mood disorders (either MDD or BD) and the MetS. We will also explore potential implications of these findings for the development of preventative and therapeutic interventions for mood and metabolic diseases.

2. Methods

This study is a narrative review investigating the associations between mood disorders, i.e. MDD and BD, and immune-inflammatory, oxidative stress and metabolic biomarkers in association with the MetS. The sources used were identified in the electronic database Medline (PubMed) and Google Scholar and were limited to the English language from 1960 until 2016. Using the MeSH (Medical Subject Headings), the following search terms were used: "depressive disorders" and "bipolar disorders" and "immune" and "inflammation"; "depressive disorders" and "bipolar disorders" and "oxidative stress" and "metabolism". We included original research, which examined diagnoses of MDD or BD in their relationships with immune-inflammatory, oxidative stress and metabolic biomarkers. We excluded articles if MDD or BD were due to other medical diseases than MetS or due to interferon alpha (IFN-α) treatment. Furthermore, review articles were searched, and other publications cross-referenced for additional published articles.

3. Results

3.1. Characteristics of Metabolic Syndrome (MetS)

MetS is one of the major public health challenges worldwide, being characterized by abdominal obesity, dyslipidemia, hyperglycemia, and hypertension, in turn contributing to an increased risk of T2DM and CVD (Alberti et al., 2009, 2005; Maes et al., 2011a). There is an approximate 24% prevalence rate of MetS in adults in the United States (Toalson et al., 2004), with variability that is dependent upon the MetS definition and ethnic group, as well as gender.

Diagnostic criteria for MetS can vary, although most consider similar risk factors, including increased central obesity as measured by waist circumference, increased glucose (insulin resistance), triglyceride levels and blood pressure, as well as lowered high density lipoprotein (HDL) cholesterol (HDL-C) (Grundy et al., 2005). The International Diabetes Foundation (IDF) diagnostic MetS criteria requires at least three out of the following five criteria to be present: 1) abdominal obesity using population and country-specific definitions, 2) hypertriglyceridemia: ≥ 150 mg/dL or on hypolipidemic agent, 3) low HDL-c: ≤ 40 mg/dL in men and ≤ 50 mg/dL in women or on hypolipidemic agent, 4) average blood pressure ≥ 130/85 mmHg or currently taking antihypertensive medication, 5) elevated fasting glucose ≥ 100 mg/dL or on oral antidiabetic medication (Alberti et al., 2009, 2005). Thus, the IDF clinical definition makes the presence of abdominal obesity necessary for diagnosis. When present, two additional factors, such as raised blood pressure, dyslipidemia with raised triglycerides and lowered HDL-C or raised fasting glucose, must also be present. It should be noted that ethnicity-specific criteria for abdominal obesity have been proposed (Alberti et al., 2009, 2005). Although a number of differences in MetS criteria have emerged, such as variations in abdominal obesity, the IDF criteria emphasize insulin resistance (Alberti et al., 2009, 2005). The American Heart Association (and the National Heart, Lung, and Blood Institute (*NHLBI*) criteria for MetS seem to have the highest associations with CVD, although all MetS criteria show a positive association with CVD (Khosravi-Boroujeni et al., 2015).

3.2. Principal components of the metabolic syndrome

As discussed above, the MetS is the clustering of an increased atherogenic lipid profile (e.g. hypertriglyceridemia and decreased HDL-c), insulin resistance, abdominal obesity and elevated blood pressure (Jamshidi et al., 2014). MetS is thus, by definition, accompanied by increased indices of atherogenicity and insulin resistance and increased abdominal circumference or body mass index (BMI). Commonly used indices to measure the atherogenic component of MetS are the atherogenic index of plasma (AIP; computed as [log10 triglycerides]/[HDL-c]), and Castelli risk index 1 and 2 (computed as [total cholesterol]/[HDL-c] and low density lipoprotein [LDL-c]/[HDL-c], respectively). These indices significantly predict vascular risk with a predictive value greater than single lipid measures (Millan et al., 2009; Nunes et al., 2015; Vargas et al., 2014a,b). AIP also reflects the presence of atherogenic LDL-c and HDL-c particles in plasma, and it is a sensitive predictor of coronary atherosclerosis and CVD risk (Onyedum et al., 2014).

Insulin resistance is the condition in which the sensitivity of insulin in target tissues is compromised (Laakso and Kuusisto, 2014). Insulin resistance can be measured by the homeostasis model assessment (HOMA) or the updated HOMA2 model, which is based on fasting plasma levels of glucose and insulin. This method allows to measure insulin resistance using HOMA2IR index, insulin sensitivity using HOMA2S% and beta-cell function using HOMA2B% (Matthews et al.,