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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.,

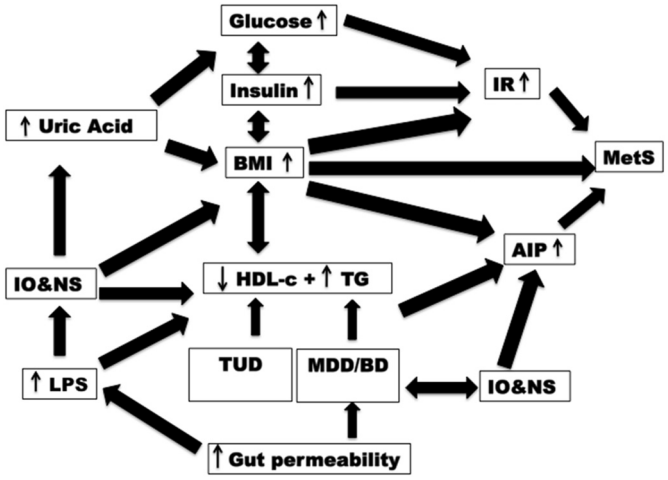

Fig. 1. Associations between the MetS, increased atherogenicity, insulin resistance, and BMI and their associations with mood disorders.

1985).

Body mass index (BMI) is defined as the weight in kilograms divided by the square of the height in meters (kg/m^2). A BMI over 30 kg/m^2, denoted as obesity, is linked with alterations in lipoprotein particle profile and insulin resistance, which may influence CVD and/or T2DM risk (Solomon and Manson, 1997; WHO, 2000).

In order to examine the principal metabolic components that delineate MetS in mood disorders we have examined the associations between MetS and atherogenicity (as measured with the AIP and Castelli risk indices), insulin resistance and sensitivity (as measured with HOMA2IR, HOMA2S and HOMA2B indices), BMI and body circumference, and blood pressure (Bortolasci et al., 2015). We established that in healthy controls and patients with mood disorders MetS is associated with three main components contributing independently to MetS, i.e. increased AIP, HOMA2IR and BMI, whereas Castelli indices, abdominal circumference and blood pressure were not significant predictors of the MetS in this logistic regression analysis after considering the effects of AIP, HOMA2RI and BMI (Bortolasci et al., 2015). BMI was additionally significantly associated with the AIP and HOMA2IR index. Fig. 1 shows the associations between the MetS, increased atherogenicity, insulin resistance and BMI. The latter was associated with increased atherogenicity and insulin resistance and thus directly (that is independently from atherogenicity and insulin resistance) and indirectly (via effects on atherogenicity and insulin resistance) with MetS (He et al., 2015). MetS may be described to reflect different pathophysiological processes comprising increased insulin resistance, atherogenicity and an increased BMI (Bortolasci et al., 2015).

We have reported that changes in AIP in depression and BD were not affected by use of psychotropic medications (Nunes et al., 2015; Bortolasci et al., 2015). Thus, no differences in atherogenic indices were detected between medicated patients and patients who were free of psychotropic drugs, while the relationships between atherogenic indices and MDD/BD were also found in patients who were drug free (Nunes et al., 2015). In the study of Bortolasci et al. (2015) no significant effects of psychotropic drugs on AIP and insulin resistance were found. Nevertheless, in the latter study there was a significant although mild effect of use of statins suppressing the AIP index, although statin use did not have a significant effect on insulin resistance.

3.3. Mood disorders and the components of the MetS

One-third of BD patients using the Adult Treatment Panel III report (ATP III) definition meet criteria for MetS (Fagiolini et al., 2005; Toalson et al., 2004; Vancampfort et al., 2013a). Several clinical studies have provided empirical evidence for the relationship between MetS and MDD and BD (Baptista et al., 2004; Herva et al., 2006; Kinder et al., 2004; Lett et al., 2004; Skilton et al., 2007; Vancampfort et al., 2013c). MDD is accompanied by typical changes in lipid metabolism including a lowered degree of esterification of serum cholesterol indicating changes in reverse cholesterol transport (Maes et al., 1994; Parikh et al., 2014) and lowered HDL-c in acute and chronic phases of MDD (Maes et al., 1997a). In our studies, there was no evidence that treatment with antidepressants could explain these findings (Maes et al., 1997a). For example, a prospective study showed that 5 weeks treatment with antidepressants did not affect serum HDL-c and other lipid concentrations (Maes et al., 1997a). Statins, the mainstay treatment for dyslipidemia in MetS, not only decreases AIP, but may also increase HDL-c levels (Bortolasci et al., 2015). Nevertheless, the specific lipid profile in MDD/BD was also detected in patients free of antidepressants and statins (Bortolasci et al., 2015). On the other hand, mood stabilizers and antipsychotics, undoubtedly contribute to weight gain in BD patients (Creta et al., 2015).

Therefore, shared metabolic risk factors between MDD and CVD are lowered serum levels of HDL-c and disorders in reverse transport of cholesterol (Maes et al., 1994; 1999b, 1997b). One study suggests that MDD, but not BD, is accompanied by increased Castelli risk indices 1 and 2 (Vargas et al., 2014a,b). On the other hand, AIP is increased in both MDD and BD, and can provide a mechanistic explanation for the links between mood disorders and atherogenesis and thus MetS and CVD (Nunes et al., 2015). However, it should be noted that lipid dysregulation is not specific to mood disorders among psychiatric conditions, being also evident in schizophrenia, with the highest levels of lipid dysregulation across these psychiatric conditions being evident in women and those aged over 40 years (Wysokinski et al., 2015).

A systematic review and meta-analysis showed a small but significant association between insulin resistance and depressive symptoms (Kan et al., 2013), with the families of BD patients also showing increased insulin resistance, as well as other MetS indicants, suggesting a role for genetic factors in the association of insulin resistance with BD (Baptista et al., 2015). Significant relationships between depression and anthropometric measurements, including BMI, have not been observed in all studies (Maes et al., 1991). Recent data indicate higher levels of BMI and obesity in mood disorder patients versus healthy controls (Vargas et al., 2014a,b; Williams et al., 2009). Being overweight or obese is prevalent in over half of BD patients, independent of psychotropic medication (Kemp et al., 2010).

A recent study found that MDD and BD are closely related to increased atherogenicy (as measured with AIP), but not to insulin resistance (as measured with the HOMA2 indices) or BMI (Bortolasci et al., 2015). Such differences may be explained by the influence of small but numerous genetic and epigenetic differences across studies, as well as by distinct definitions of BD and MDD e.g. via structured interview versus self-report scales. But most importantly, the study of Bortolasci et al. (2015) statistically adjusted the data for effects of intercorrelations between atherogenicity, insulin resistance and BMI and thus examined the specific and cumulative effects of each predictor variable increasing risk of the MetS. Fig. 1 shows the associations between the MetS, increased atherogenicity, insulin resistance and BMI, and their associations with mood disorders. Thus, mood disorders are associated with lowered HDL-c levels and increased triglyceride levels and consequently with increased atherogenicity, but not with insulin resistance. As such, we established atherogenicity was the only shared factor between mood disorders and MetS, whereas insulin resistance and BMI were not relevant to mood disorders (Bortolasci et al., 2015).

As we will explain below, increased levels of uric acid, and activated IO & NS pathways, including those resulting from leaky gut, further contribute to different aspects of the atherogenicity and insulin resistance potential. Thus, BD and MDD, and BMI together with elevated levels of uric acid and IO & NS pathways independently,

contribute to increased atherogenic potential as measured by the AIP (Bortolasci et al., 2015).

3.4. Role of uric acid in the metabolic syndrome

Increased uric acid is a highly significant risk factor for increased insulin resistance and atherogenic potential, and thus MetS. Firstly, epidemiological studies show a significant association between uric acid, insulin resistance and MetS (Feoli et al., 2014), with MetS being associated with a very high incidence of hyperuricemia (Choi and Ford, 2014; Facchini et al., 1991). Insulin resistance (and thus MetS) shows a significant positive correlation with uric acid (Bortolasci et al., 2015; Feoli et al., 2014). Bortolasci et al. (2015) reported that this association was independent from use of psychotropic drugs or statins. Uric acid elevation may be a risk factor for the onset phase of T2DM (Miyake et al., 2014). Some authors also reported positive correlations between uric acid, on the one hand, and BMI, obesity and insulin resistance, on the other (Fabbrini et al., 2014). Moreover, increased uric acid levels were associated with an increased AIP index (Baliarsingh et al., 2012; Lippi et al., 2010), while there were inverse relationships between uric acid and HDL-c levels (Chu et al., 2000; Lin et al., 2006; Onat et al., 2006).

Secondly, increased levels of uric acid may precede the onset of obesity, insulin resistance, diabetes, hypertension and inflammatory responses (Johnson et al., 2013), while lowering the levels of uric acid may improve insulin resistance (Ogino et al., 2010). Uric acid may cause insulin resistance via different mechanisms: a) Increased uric acid contributes to liver insulin resistance by enhancing mitochondria oxidative stress (Lanaspa et al., 2012), b) Uric acid causes oxidative stress in pancreatic islets cells and consequently islet cell dysfunction (Roncal-Jimenez et al., 2014), and c) Uric acid induces inflammatory responses in adipose cells and lowers adiponectin production (Baldwin et al., 2011). In animals, uric acid regulates hepatic steatosis and insulin resistance via nucleotide-binding oligomerization domain (Nod), Nod-Like Receptors (NLR) family, pyrin domain containing 3 (NLRP3) inflammasome-dependent mechanisms (Wan et al., 2016). This gives the regulation of insulin resistance another link to IO & NS, given that reactive oxygen species (ROS) is a significant regulator/activator of the NLRP3 inflammasome (Han et al., 2015), with resultant pro-inflammatory cytokines produced, interleukin (IL-1β) and IL-18, contributing to pro-inflammatory activation. The NLRP3 inflammasome may be at the interface of the interaction of inflammation and oxidative stress in MetS (Han et al., 2015).

Given that uric acid contributes to plasma free-radical scavenging capacity, it is suggested that increased uric acid in MetS is an adaptive mechanism preventing oxidative damage caused by free radicals (Fabbrini et al., 2014). However, this would not seem a bit simple as, although uric acid is a strong antioxidant in the plasma, it has pro-oxidant properties in many cells (Lanaspa et al., 2012; Sautin and Johnson, 2008). Increased levels of insulin also cause urate absorption in the proximal tubule and may contribute to hyperuricemia. Therefore, it may be concluded that there are reciprocal relationships between hyperinsulinemia and hyperuricemia in individuals with MetS.

Previous studies showed increased uric acid levels in BD (Albert et al., 2015) and lower uric acid in MDD (Chaudhari et al., 2010; Wen et al., 2012). Nevertheless, we were unable to find any changes in uric acid between patients with MDD and BD and normal controls (Bortolasci et al., 2015). Allopurinol, the prototypical uric acid lowering agent, appears to have equivocal effects in mood disorders, with positive and negative trials published (Jahangard et al., 2014; Machado-Vieira et al., 2008; Weiser et al., 2014). Aging and increased microbial activity, both risk factors for MetS in mood disorders, trigger NLRP3 inflammasome activation, which can be alleviated by melatonin (Volt et al., 2016). Decreased melatonin is a genetic risk factor for mood disorders, especially BD (Anderson and Maes, 2015a,b), but also MDD, where it may act to modulate IL-6 trans-signaling (Anderson et al., 2013), with IL-6 being highly produced by adipocytes and IL-6 trans-signaling causing recruitment of macrophages into adipose tissue (Kraakman et al., 2015).

3.5. IO & NS pathways in mood disorders

BD and MDD are associated with increased levels of acute phase proteins, including C-reactive protein (CRP) and haptoglobin, adhesion molecules and complement factors (Maes, 2008). The complement system has a significant function in innate and adaptive immune pathways and alterations in complement factor H (CFH), which acts as a regulator of the alternative pathway of the complement cascade (Zhang et al., 2016). Another interesting finding is that a polymorphism of CFH gene, rs1061170, has been associated with younger age at onset of MDD in a Chinese population showing the complexity interaction between the genome and mood disorders (Zhang et al., 2016).

Cytokines are soluble mediators released by a variety of cells, both at the periphery by macrophages and lymphocytes as well as centrally by astrocytes and microglia, which act either synergistically or antagonistically. Inflammation, as measured by pro-inflammatory cytokines and chemokines, is an important predictor of the course of BD, perhaps especially of depressive relapse (Bond et al., 2015). Excessive and/or prolonged activation of cytokine networks in the central nervous system (CNS) can promote an interconnected suite of abnormalities that are relevant to diminished neurotrophic support, decreased neurogenesis, increased glutamatergic activation, oxidative stress and astrocyte apoptosis as well as dysregulation of glial/neuronal interactions and cognitive dysfunction (Maes, 2009; Miller et al., 2009). The reduction in neuroprotective markers, which indicates an impaired neuroprotection, might play an important role in the pathophysiology of major depression (Myint et al., 2006).

Oxidative and nitrosative stress can result from either diminution of antioxidant defenses or increased production of reactive nitrogen species (RNS) or reactive oxygen species (ROS) that are constantly produced in the context of mitochondrial energy generation (Andreazza et al., 2008; Berk et al., 2008). An imbalance between oxidant and antioxidant mechanism contributes to accumulation of ROS/RNS, inducing damage to deoxyribonucleid acid (DNA), proteins, lipids and mitochondria which in turn may contribute to telomere shortening and neuronal degradation (Andreazza et al., 2008; Moylan et al., 2014).

Alterations in antioxidant enzymes in BD have been reported with increases in superoxide dismutase (SOD) activity during the manic and depressed phases of BD and decreased catalase (CAT) activity in euthymic patients with BD (Andreazza et al., 2007). Additionally, high SOD levels were evident in the prefrontal cortex (PFC), but not in the hippocampus, in postmortem MDD patients versus healthy controls (Michel et al., 2007). Patients during acute depressive episodes have significantly higher activity levels of antioxidant enzymes, such as SOD and CAT, than healthy controls (Gałecki et al., 2009). This was in accordance with another study which found a significant increase in serum SOD in patients with MDD in comparison to healthy controls (Khanzode et al., 2003).

Antioxidant defenses, such as lowered HDL-c, zinc and coenzyme Q10 (Morris et al., 2013), as well as vitamin D and E levels were found in MDD patients and contribute to the detrimental effects of increased IO & NS (Maes et al., 2011b). Zinc, for example, is a trace element and an important co-factor for various enzymes as well as being necessary for DNA synthesis, protein conformation, membrane stabilization and membrane protection against lipid peroxidation (Maes et al., 1999d). There are different mechanisms that explain the role of zinc in promoting positive effects, including protection conferred by zinc against the production of inflammatory cytokines and IO & NS activation (Connell et al., 1997; Maes et al., 2011e). Paraoxonase 1 (PON1) is a potent antioxidant, which protects against lipid peroxidation (Bortolasci et al., 2014a,b; 2015). Plasma PON1 activity is lower in patients with mood disorders, either BD or MDD (Bortolasci et al.,

2014a,b).

A meta-analysis indicates that patients with BD have increased lipid peroxidation, as assessed by elevated levels of thiobarbituric acid reactive substances (TBARS) (Andreazza et al., 2008). Patients suffering from acute depressive episodes have significantly higher levels of MDA than healthy controls (Gałecki et al., 2009; Khanzode et al., 2003; Maes et al., 2011d). Another indicant of increased lipid peroxidation in MDD is that serum oxidized LDL (OxLDL) antibodies are increased in MDD as compared to normal controls (Maes et al., 2010). Another study in patients with BD in remission did not find a correlation with cognitive impairment and O & NS biomarkers (MDA, SOD) and these findings suggest that O & NS levels may be more related to state than trait markers of this disease (Aydemir et al., 2014).

Depression is also accompanied by signs of nitrosative and nitro-oxidative stress. MDD is accompanied by signs of hypernitrosylation (that is nitric oxide (NO) or nitroso-binding to proteins) and auto-immune responses to NO adducts (Maes et al., 2013b; Maes et al., 2011c). NO is an important driver of many central processes, although high levels are associated with neuronal damage and apoptosis (Morris et al., 2016), with the increased levels of NO in MDD being linked to cognitive impairment (Talarowska et al., 2012). There is also evidence that MDD is accompanied by increased protein nitration (that is binding of a nitrogen dioxide (NO_2) molecule to proteins). For example, a comparison study of the early and late stages of BD with healthy controls, indicates that those in the late stage of illness showed increased activity of 3-nitrotyrosine with increased levels of 3-nitrotyrosine evident in the early stage of illness (Andreazza et al., 2009). Plasma nitric oxide by-products (NOx) levels are significantly higher in suicidal depressive patients than non-suicidal depressive patients or healthy controls (Kim et al., 2006). This is in accordance with another study, in which individuals with a history of suicide attempts had significantly higher levels of NOx and lipid hydroperoxides and lowered total radical trapping antioxidant parameter (TRAP), as compared to individuals without suicide attempts (Vargas et al., 2013b). Increased nitrosylation and nitration in MDD may be the consequence of an increased production of NO by increased production of inducible nitric oxide synthase (iNOS) (Gałecki et al., 2012; Jankovic et al., 2016).

There is now also evidence that increased gut permeability (leaky gut) and the consequent increased translocation of gram-negative commensal bacteria may play a role in the pathophysiology of MDD (Maes, 2008). Thus, these authors detected that depression is accompanied by increased IgM and IgA responses to a number of gram-negative commensal bacteria suggesting increased bacterial antigens and endotoxin (lipopolysaccharide, LPS) in the peripheral blood and mesenteric lymph nodes. Moreover, the same authors reported that there are, in MDD, significant relationships between increased IgA/IgM responses to commensal bacteria (indicating leaky gut) and signs of immune activation and O & NS (Maes et al., 2013a). It is known that LPS may activate a signaling cascade that elicits pro-inflammatory responses through activation of the Toll-Like Receptor 4 (TLR4) complex (Lucas and Maes, 2013a).

Also life style factors, such as physical activity and diet, may be associated with activated IO & NS pathways in MDD and BD. Lack of physical activity has been recognized as a major health problem in many countries, especially for the population that are living in urban centers (WHO, 2003). In a community-based study, lower levels of physical activity in childhood were associated with depression in adulthood (Jacka et al., 2011). IO & NS pathways are activated in people with a sedentary lifestyle, possibly increasing the risk to develop mood disorders in this population (Gomes et al., 2012; Moylan et al., 2014). However, a healthy dietary pattern was associated with a reduced likelihood of depressive symptoms, especially for those co-morbid with T2DM (Dipnall et al., 2015) with the consumption of nutrient-dense foods, modulating depression, although not anxiety disorders (Jacka et al., 2012). As such, variations in diet are likely to interact with factors such as physical inactivity that increased depression, at least in part, via IO & NS regulation.

3.6. Review of IO & NS pathways in MetS

Adipose tissue induces chronic latent inflammation via adipokines and pro-inflammatory cytokines. Adipokines influence satiety sensation and pancreatic insulin responses (Lemche et al., 2016). The chronic low-level inflammation in adipose tissue is based on T-cell and macrophage accumulation (Pavlov and Tracey, 2012). An activated HPA axis with increased cortisol levels can contribute to the development of obesity and insulin resistance in MetS subjects (Lemche et al., 2016; Pavlov and Tracey, 2012). Moreover, increased levels of acute phase proteins, including CRP (Hosseinzadeh-Attar et al., 2016) and haptoglobin (Hamalainen et al., 2012), adhesion molecules (Guarner and Rubio-Ruiz, 2014) and complement factors (Vlaicu et al., 2016) also are found in MetS patients. Interestingly, high levels of CRP are associated with cognitive dysfunction in subjects with MetS (Dik et al., 2007). Complement proteins can be synthesized by adipose tissue and can modulate lipid metabolism and hyperglycemia (Vlaicu et al., 2016). Furthermore, adipose tissue also produces pro-inflammatory cytokines like IL-6 and TNFα, and activated nuclear factor-kappa B (NF-κB) pathways (Lemche et al., 2016).

Oxidative stress pathways have emerged as playing a central role in MetS (Hutcheson and Rocic, 2012; Rani et al., 2016). Increased levels of MDA have been described in subjects with MetS, obesity and MDD (He et al., 2009; Maes et al., 2011e; Sankhla et al., 2012). One of the main criteria found in different definitions of MetS are the dysfunctions in lipid metabolism evidenced by low levels of HDL-c and high levels of triglycerides (Alberti et al., 2009). It is also known that HDL-c has a significant antioxidant activity and therefore lowered levels of HDL-c in the MetS may be one of the several mechanisms explaining activated IO & NS pathways (Hutcheson and Rocic, 2012). In MetS subjects, PON1 activity is lowered and is associated with an increased lipid peroxidation (Senti et al., 2003). PON1 Q192R genotypes and interactions between genotypes X smoking are risk factors for MetS which together with lowered HDL-c and increased body mass and age may contribute to MetS (Bortolasci et al., 2014a,b). Patients with insulin resistance have high MDA levels and associated waist-to-hip ratio (Lee, 2001).

Obesity has been associated with an increased production of NO produced by increased iNOS (Jankovic et al., 2016). This process can be potentialized by impaired NOS activity in adipocytes following insulin resistance (Rani et al., 2016). NO has a key central regulator of energy metabolism responding to imbalances in insulin sensitivity in adipose tissue (Litvinova et al., 2015). There is also a significant association between MetS and increased NOx (Caimi et al., 2012; Ghasemi et al., 2013).

Dysfunctions in others antioxidant defenses include changes in SOD, catalase and glutathione peroxidase (GpX) activity (Baez-Duarte et al., 2016). Furthermore, decreased levels of glutathione (GSH) can occur in the MetS leading to enhanced ROS formation (Bonomini et al., 2015). In physiological conditions, pancreatic β-cells have relatively reduced antioxidant levels, including GpX and catalase, and due to a high metabolic activity are more vulnerable to oxidative stress leading to dysfunctions in insulin pathways (Keane et al., 2015). Furthermore, polymorphisms in genes that codify for antioxidant enzymes including superoxide dismutase (SOD), catalase and glutathione peroxidase (GpX1) are directly related to hypertension (Bonomini et al., 2015; Mansego et al., 2011).

The underlying stimulus for these metabolic derangements in obesity are not fully elucidated, however recent evidence in rodents and humans suggests that systemic, low level elevations of gut derived LPS may play an important role in obesity related, whole-body and tissue specific metabolic perturbations. Low-grade elevation in plasma LPS has been termed “metabolic endotoxemia” and this state is associated with a heightened pro-inflammatory and oxidant environ-

ment often observed in obesity. Given the role of inflammatory and oxidative stress in the etiology of obesity related cardio-metabolic disease risk, it has been suggested that metabolic endotoxemia may serve a key mediator of metabolic derangements observed in obesity (Boutagy et al., 2016).

4. Interconnections between IO & NS and metabolic pathways in the MetS and mood disorders

Activated IO & NS pathways and a pro-atherogenic lipid profile are found in mood disorders and the MetS. These conditions are accompanied by increased levels of pro-inflammatory cytokines, lipid peroxidation biomarkers, including MDA, and lowered levels of antioxidants, such as HDL-c, zinc and PON1, and increased atherogenic indices, including Castelli risk indices 1 and 2 and AIP (Nunes et al., 2015; Vargas et al., 2014a,b). We will now discuss some interconnected IO & NS and lipid pathways that may underpin the associations between MetS and mood disorders.

4.1. O & NS and lipid metabolism

As discussed above, shared metabolic risk factors between mood disorders with MetS and CVD include lowered serum levels of HDL-c, disorders in the reverse transport of cholesterol esters and lowered levels of n-3 polyunsaturated fatty acids (PUFAs) (Maes et al., 1994, 1998, 2011e; Nunes et al., 2013a,b,c). The increased production of ROS by monocytes/macrophages, endothelial and vascular smooth muscle cells is an important factor in the early phases of CVD (Bortolasci et al., 2015; Fearon and Faux, 2009). Importantly, oxidative stress may oxidize HDL-c, which may have adverse consequences because HDL-c has anti-inflammatory, antioxidant and antithrombotic properties, as well as additionally transporting excess cholesterol to the liver (reverse cholesterol transport), thereby decreasing the cholesterol load and associated vascular inflammation (He et al., 2013a; Linsel-Nitschke and Tall, 2005). These oxidative processes, occurring in MetS and mood disorders, may modify LDL-c into oxidized-LDL due to prevalent oxidative conditions during both disorders. Increased levels of oxidized LDL-c in the blood circulation indicate higher risk for atherosclerosis and myocardial infarction (Bonomini et al., 2015). Increased oxidized-LDL antibodies are observed in atherosclerosis and depressed patients (Hulthe, 2004; Maes et al., 2010; Steinerova et al., 2001). By inference, depressed patients who have significantly increased serum oxidized-LDL antibodies (Maes et al., 2010) have increased lipid peroxidation and associated autoimmune responses directed against the neoepitopes exposed when lipids are damaged. Increased serum oxidized LDL antibodies also indicate that those depressed patients are at risk for atherosclerosis or have already developed atherosclerotic lesions (Maes et al., 2010; Maes et al., 2011e). This is supported by data showing that youth with BD or MDD have increased risk of early CVD (Goldstein et al., 2015).

During LDL oxidation, neoepitopes are formed that are strongly immunogenic and may result in the generation of IgG and IgM-mediated autoimmune responses (Mandal et al., 2005). IgG autoantibodies against oxidatively modified LDL reflect the effects of O & NS and lipid peroxidation in vivo. The oxidized LDL IgG autoantibodies are probably pro-atherogenic (Gounopoulos et al., 2007) and their presence predicts myocardial infarction and progression of carotid atherosclerosis (Maes et al., 2011e; Vaarala, 2000). Depression and CVD are additionally accompanied by increased oxidation of phospholipids which is another factor underpinning increased atherogenicity in mood disorders (Maes et al., 2011a).

MDA is a reactive aldehyde or reactive carbonyl compound that may modify proteins to generate advanced lipoxidation and ALE products. MDA is employed as a measure for lipid peroxidation and thus also for oxidative stress. ALEs have detrimental effects as they are pro-inflammatory, weaken the antioxidant defenses, and impair DNA repair (Maes et al., 2011e). ALEs additionally play significant roles in atherosclerosis and neurodegenerative disorders (Maes et al., 2011e). Evidence is now accumulating that ALEs cause atherosclerosis progression, as they are pro-inflammatory, weaken the antioxidant defenses, and impair DNA repair (Aldini et al., 2007; Maes et al., 2011e). MDA is also capable of modifying LDL-c into MDA-LDL (malondialdehyde-modified-LDL), which is a chemical modification of LDL-c that reflects LDL-c peroxidation. MDA-LDL levels are significantly increased in atherosclerotic patients with elevated intima media thickness (Kametsu et al., 2005; Maes et al., 2011d). MDA-LDL may stimulate the accumulation of cholesterol esters in macrophages, which in turn can contribute to foam cell formation within atherosclerotic lesions (Gonen et al., 1987; Maes et al., 2011d). MDA has inhibitory effects on the nucleotide excision repair system through direct interactions with cellular repair proteins. This indicates that MDA sensitizes mutagenesis through DNA damage and inhibitory effects on DNA repair (Feng et al., 2006; Maes et al., 2011d).

In addition, MDD is accompanied by increased IgM-mediated autoimmune responses directed to MDA, indicating increased MDA formation and a natural autoimmune response to MDA aimed at counteracting the damage caused by lipid peroxidation (Moylan et al., 2014). Interestingly, there is also some evidence that T2DM and diabesity may be accompanied by autoimmune responses, including autoimmune responses directed against β cells and consequent accelerated β-cell death, the presence of self-reactive T cells and defects in regulatory T cells (Itariu and Stulnig, 2014). This condition is also labelled as autoimmune diabetes of the adult (LADA).

4.2. Antioxidants: zinc and PON1

Lowered serum zinc concentrations are detected in CVD patients and may be a risk factor for the development of CVD (Ghayour-Mobarhan et al., 2008; Maes et al., 2011e). Zinc deficiency plays a critical role in atherosclerosis particularly in patients who are genetically predisposed to develop activated IO & NS pathways. This may be explained as zinc is critical for the maintenance of vascular endothelial cell integrity during inflammation and because lower zinc may endanger the elongation of PUFAs thus causing lowered ω3 PUFAs (Maes et al., 1999c, 2011e; Meerarani et al., 2000). Zinc also interferes with peroxisome proliferator activate receptors (PPAR) transactivation activity, which is important since PPAR can inhibit pro-inflammatory NF-κB signaling (Maes et al., 2011e; Shen et al., 2008). Another mechanism whereby zinc reduces the atherogenic burden is by reducing iron-catalyzed free radical reactions (Jenner et al., 2007; Maes et al., 2011d). However, it should be noted that zinc when derived from red meat may increase CVD and depression (de Oliveira Otto et al., 2012), suggesting that the source of zinc may be relevant.

PON1 is an enzyme synthesized in the liver and secreted into plasma where it is bound to HDL particles. PON1 has strong antioxidant properties and is associated with HDL particles resulting in a PON1-HDL-c complex that protects HDL-c and LDL-c against oxidation (Ceron et al., 2014). By inference, PON1 protects against the key processes underpinning the pathophysiology of atherosclerosis (Bortolasci et al., 2014a,b). As described, plasma PON1 activity is lower in patients with BD, MDD and MetS especially when comorbid with nicotine dependence or tobacco use disorder (TUD). Lowered PON1 activity in both mood disorders and MetS may therefore result in decreased protection against oxidative damage of HDL-c and LDL-c which together with increased oxidative stress could lead to the increased oxidized-LDL and HDL-c and thus lowered HDL-c levels and increased atherogenicity (Bortolasci et al., 2014a,b). Recently, we observed that lowered PON1 activity in mood disorders is associated not only with lowered HDL-c levels and an increased Castelli risk 1 index but also with lowered quality of life, more disability and increased severity of depression and anxiety (Moreira et al., submitted).

4.3. Bacterial translocation and the TLR radical cycle

Under normal conditions the immune system is functionally and geographically separated from the gram-negative commensal gut bacteria by intact tight junctions binding gut epithelial cells. However, many factors can act to increase the permeability of the gut, by loosening tight junctions, including dietary facts such as saturated fats and alcohol, stress-induced cortisol (Martin-Subero et al., 2016), and neurodegenerative conditions such as Parkinson's disease (Anderson et al., 2017b, in press) and multiple sclerosis (Anderson et al., 2017a, in press). Also obesity is associated with altered gut microbiota composition (Konrad and Wueest, 2014). Diets rich in fat or low in fiber can change the microbiome and consequently impair gut barrier function (Konrad and Wueest, 2014).

Under conditions of increased gut permeability, gram-negative bacteria (and tiny partially digested food particles) can translocate over the gut into the mesenteric lymph nodes (MLNs) or the blood stream (Leonard and Maes, 2012). Once these bacteria are translocated, immunocytes can mount an IgA or IgM-mediated immune response directed against such foreign body invasion (Muraca et al., 2015). This alteration in the gut system, together with interrelated mesenteric adipose tissue inflammation can promote high levels of bacteria and bacteria-derived factors, pro-inflammatory cytokines and lipids into the portal circulation, resulting in the development of (hepatic) insulin resistance (Konrad and Wueest, 2014). Clinically depressed patients display higher IgM and IgA responses to LPS and antigens of gram-negative bacteria as a result of increased bacterial translocation, leading to the production of oxidative and nitrosative stress and pro-inflammatory cytokines (Lucas and Maes, 2013a). These processes in turn may disrupt the blood–brain barrier, leading to increased leukocyte infiltration into the central nervous system (Anderson et al., 2017b), which may contribute to processes of neuroprogression in mood disorders and other central conditions (Maes, 2008; Maes et al., 2012). Moreover, extracellular vesicles derived from gut commensal bacteria, called gut microbiota-derived outer membrane vesicles, can enter the blood and the brain thereby eliciting immune responses in the periphery and the brain as well (Muraca et al., 2015).

The activated inflammatory and oxidative pathways and increased bacterial translocation in both mood disorders and MetS may result in activation of a common pathway, i.e. the Toll-Like Receptor (TLR). Pattern recognition receptors (PRRs), which include TLR2 and TLR4, are an important part of the host defense system. PRRs recognize pathogen-associated molecular patterns (PAMPs) and damage associated molecular patterns (DAMPs). TLRs recognize mycoplasma, fungus and viruses as well as LPS, a typical PAMP derived from gram-negative bacteria (Garate et al., 2013). Psychosocial stressors, also, may additionally upregulate TLR4 expression or activation (Lucas and Maes, 2013b).

The formation of redox-derived DAMPs, including MDA, oxidized LDL and oxidized phospholipids, may consequently activate the TLR4 complex, a phenomenon described as the TLR Radical cycle (Lucas and Maes, 2013a; Lucas et al., 2015). Through binding with the TLR2 and TLR4 complexes, LPS activates different intracellular signaling molecules, including NF-*k*B and MAPK, thereby increasing expression of IO & NS genes (Lucas and Maes, 2013a; Lucas et al., 2015). LPS additionally activates the NOx family of NADPH oxidases, which, in turn, increases production of iNOS, NO, superoxide and peroxides as well as reducing the levels of CC16 and uteroglobin, an endogenous anti-inflammatory substance, which is lowered in depressed patients (Maes et al., 1999a). This is relevant to depression, as LPS administration increases nitrite, nitrate and MDA levels whilst decreasing brain GSH levels. Increased bacterial translocation also plays a role in the pathophysiology of congestive heart failure (CHF) and CVD (Maes et al., 2011d). Increased bacterial translocation is associated with CVD not only through activated IO & NS pathways as explained above, but also through direct modulation of cardiac cells, which express TLR2 and TLR4 (Maes et al., 2011e). This explains that bacterial translocation may be accompanied by increased production of pro-inflammatory cytokines (Meng et al., 2008) and NF-κB (Zang et al., 2007) in myocardial cells. Increased leaky gut and bacterial translocation may also trigger gut-derived inflammation which may become chronic and induce cardiosuppression, which subsequently worsens clinical symptoms of CVD and predicts increased mortality (Charalambous et al., 2007; Sandek et al., 2008). The attenuation of bacterial translocation, through antibiotic-induced intestinal decontamination can reduce stress-induced neuroinflammation, indicating that stress-induced neuroinflammation is at least partially caused by increased bacterial translocation (Anderson and Maes, 2015a,b; Moylan et al., 2014). Bacterial decontamination of the gut and thus the subsequent decrease in bacterial translocation improve also the condition of heart disease patients (Charalambous et al., 2007). Finally, activation of the TLR-Radical Cycle may cause chronic inflammation and especially chronic O & NS, which may further aggravate the immune pathophysionlogy of mood disorders and MetS.

4.4. BMI and adipocytes

Increased BMI can lead to a high atherogenic lipid profile and insulin resistance, which both strongly predict MetS (Bortolasci et al., 2015). In addition, elevated BMI is a significant contributor to activated immune-inflammatory pathways also in BD, more so even than recent mood illness severity (Bond et al., 2015). During obesity, enlarged mature adipocytes can activate macrophages in the expanded adipose tissue, leading to the release of pro-inflammatory cytokines that cause a chronic and low-grade inflammatory state. Those changes are metabolically toxic and thus, can interfere with the regulatory network of neural circuits, impair the differentiation of pre-adipocytes and contribute to excessive lipid storage in other tissues (Gustafson et al., 2009; Moylan et al., 2014). Enlarged adipocytes may prevent the adequate diffusion of oxygen from blood vessels, leading to adipose tissue hypoxia, which acts with low-grade inflammation, to mediate ethanol induced glucose intolerance (He et al., 2015). However, recent work in murine enlarged adipocytes shows such lipid-overload to provoke insulin resistance independent of inflammation (Kim et al., 2015).

Adipocytes produce biologically active molecules known as adipokines (or adipocytokines) that have pro-inflammatory or anti-inflammatory effects, including leptin and adiponectin. Leptin is a pro-inflammatory cytokine that plays a key role in regulating energy intake and expenditure and signals the brain when adipocytes become enlarged to modify appetite and behavior modifications (Jequier, 2002). Circulating levels of leptin and TNF-α are elevated in obesity and raised levels of both factors have been reported in depression (Pasco et al., 2008). As with insulin, raised levels of leptin can lead to leptin resistance, which is evident in BD and MDD with atypical features (Mansur et al., 2016; Milaneschi et al., 2015). By contrast, adiponectin levels, which have anti-inflammatory effects, may be reduced in obesity and depression (Leo et al., 2006; Ryo et al., 2004). Adipose tissue dysregulation is considered an important source of ROS (Furukawa et al., 2004), with overweight patients with MetS having elevated levels of advanced oxidation products (AOPP) and TRAP compared to healthy controls (Venturini et al., 2012). As such, the complexity of different genetic, epigenetic and environmental contributions to BMI and MetS are likely to partially overlap with MDD and BD, in turn contributing to variations in their associations with IO & NS (Anderson et al., 2016; Anderson and Maes, 2014). The above findings may explain that the relationship of BMI with MDD and BD, reported in some but not all studies, may be mediated, in part, by wider aspects of IO & NS (Bortolasci et al., 2015; Mokdad et al., 2003; Vargas et al., 2013a).

4.5. Sirtuins

Sirtuins (SIRTs) influence a broad range of cellular metabolic processes and shows different subcellular localization (Song and Kim, 2016). Silent information regulator T1 (SIRT1) exists in the nucleus (Morris et al., 2011) and has mitochondrial regulatory, neuroprotective (Mallick and D'Mello, 2014) and anti-inflammatory functions (Ye et al., 2013). SIRT1 also has effects on neurotransmitter modulation by regulation of monoamine oxidases MAO-A (Libert et al., 2011) and contributes to the regulation of glucose (Mortuza et al., 2013) and lipid metabolism (Lomb et al., 2010), thereby linking SIRT1 to important pathways responsible for body metabolism (Song and Kim, 2016). Moreover, the circadian system controls important brain systems that regulate affective and metabolic functions (Barandas et al., 2015). Sleep disorders have been related to increasing risk of both metabolic and psychiatric disorders, including obesity, type 2 diabetes, depression and suicide (Depner et al., 2014; Robillard et al., 2013). Chronic cortisol levels and HPA axis dysfunction has been identified as a common pathway between diabetes, obesity, and mood disorders (Nicolaides et al., 2014). The CLOCK and BMAL1, core components of the clock machinery, have important functions in the regulation of gluconeogenesis and lipid metabolism and can be modulated by SIRT1 (Barandas et al., 2015; Orozco-Solis and Sassone-Corsi, 2014).

5. Not only mood disorders but also the MetS may cause neuroprogression

Neuroprogression is the progressive process of IO & NS-related changes in increased neurotoxicity, excitotoxicity and apoptosis and reduced neurogenesis and neuronal plasticity (Berk et al., 2011; Bortolato et al., 2016a,b; Maes et al., 2013b; Moylan et al., 2013). Longer and more frequent mood episodes appear to increase vulnerability to further relapse, facilitating an accelerating and progressive illness course associated with functional decline (Berk et al., 2011; Moylan et al., 2013). Many pathways can contribute to the development of neuroprogression in mood disorders, like the increased levels of pro-inflammatory cytokines and cell-mediated immune (CMI) cytokines, which lead to the increased HPA axis activation and triggering of the indoleamine 2,3-dioxygenase (IDO) pathway (Maes et al., 2007). TRYCATs exert direct effects on mitochondria increasing oxidative stress and impairing mitochondrial energy production, leading to decreased synthesis of serotonin and neurotrophins (Moylan et al., 2013). These effects increase the individual's vulnerability to develop further episodes characterized by progressive neuro-cognitive and functional decline (Talarowska et al., 2016). MetS has been associated with an enhanced risk of stroke and deficits in many cognitive domains (Arenillas et al., 2007; Yates et al., 2012). For example, in hypertensive elderly subjects, MetS predicts an accelerated decline in cognitive function after one year (Viscogliosi et al., 2016). Older adults with MetS and a history of depression appear to have adverse impacts on cognition probably induced by activated IO & NS pathways (Chang et al., 2014; Viscogliosi et al., 2013). However, inconsistent results have been shown for the association between MetS and dementia (Trevino et al., 2015). Age appears to be a confounding factor in the association between the MetS and cognitive decline with regards to activated IO & NS pathways (Siervo et al., 2014; Tucsek et al., 2013). It is important to add that high calorie intake can contribute to the development of a neurodegenerative process with cognitive failure in animals, suggesting complex interactions between the different factors involved (Trevino et al., 2015).

6. Comorbid mood disorders, tobacco use disorder (TUD) and MetS

The co-occurrence BD/MDD and MetS with TUD is common and these diseases share genetic, inflammatory and oxidative stress pathways (Bortolasci et al., 2014a,b; Nunes et al., 2013a; Nunes et al., 2015). The prevalence of current smoking in BD is 68.8% and in MDD is 36.6%; however, the lifetime prevalence of smokers is about 82.5% in BD and 59% in MDD (Lasser et al., 2000). The mortality from tobacco-related diseases is about 50% in patients diagnosed with MDD and 48% in BD (Callaghan et al., 2014). MetS has been reported to be more frequent in active smokers than in those who had never smoked or had quit smoking (Chen et al., 2008). The co-occurrence of TUD and BD is considered to exemplify gene-environment interactions, where most traits fall on a continuum between genetic and environmental factors (Heffner et al., 2011).

As to the lipid profile, it is well known that cigarette smoking increases plasma levels of LDL-c, total cholesterol, and triglycerides, but decreases HDL-c (Takata et al., 2014). Cigarette smoking can alter the critical enzymes of lipid transport, lowering lecithin: cholesterol acyltransferase (LCAT) activity and changing cholesterol ester transfer protein (CETP) and hepatic lipase activity, which attributes to its impact on HDL-c metabolism and HDL-c subfractions distribution (He et al., 2013b). Also, HDL-c is susceptible to oxidative modifications by cigarette smoking, which makes HDL-c become dysfunctional and lose its atheroprotective properties in smokers (He et al., 2013b).

Also, in our studies we found that comorbid TUD and mood disorders was accompanied by significantly increased atherogenicity (as measured with AIP) as compared with TUD or mood disorders, alone (Nunes et al., 2015). These effects are attributable to the combined and cumulative effects of mood disorders and TUD lowering HDL-c levels. Fig. 1 shows the cumulative effects of TUD and mood disorders lowering HDL-c levels and thus increasing atherogenicity in comorbid TUD and mood disorders.

Patients with comorbid mood disorders and TUD exhibit alterations in levels of IO & NS biomarkers, including increased NOx, lipid hydroperoxides, AOPP and lower levels of TRAP compared to non-depressed never smokers (Vargas et al., 2013a). Plasma PON1 activity is significantly lower in patients with mood disorders comorbid with TUD than in mood disorders or TUD alone, while smoking significantly lowers PON1 activity (Bortolasci et al., 2014a,b).

Regarding shared genetic risks, several overlapping candidate genes for TUD and mood disorders have been identified, including genes that encode: 1) catechol-*O*-methyltransferase (COMT); 2) the dopamine transporter; and 3) the serotonin transporter (McEachin et al., 2010). Genetic polymorphisms of the glutathione-S-transferase theta-1 (*GST-T1*) and glutathione-S-transferase μ-1 (*GSTM1*) can lead to a lack of these enzymes that play a key role in cellular detoxification (Hayes and Pulford, 1995). Some genetic polymorphisms in TUD and BD and MDD are associated with glutathione S-transferase, such as *GSTM1* and *GSTT1*, and the *STIn2VNTR* polymorphism of the serotonin transporter (5-HTT), involving a variable number of tandem repeats in the functional 5-HTT intron (Nunes et al., 2015). Gene variants of 5-HTT have been associated with TUD comorbid with mood disorders, either BD or MDD. The *STin2VNTR* has been associated with mood disorders and TUD (Pizzo de Castro et al., 2015). The STin2.12 allele was described as positively associated with the co-occurrence of TUD and DD and BD while the STin2.10/10 genotype was described as negatively associated with it (Pizzo de Castro et al., 2015).

7. New drug targets in comorbid MDD/BD and the MetS

Fig. 2 shows the complex inter-relationships of MetS with BD/MDD and IO & NS pathways. Based on our review we conclude that shared pathways underpinning the MetS and mood disorders are activated IO & NS pathways together with increased atherogenicity, which is strongly associated with lowered HDL-c levels. These findings suggest that the association between IO & NS and metabolic pathways may be new drug targets that may contribute to the development of novel treatments for comorbid mood disorders and MetS. This may highlight new opportunities for combinatorial treatments with antidepressants in

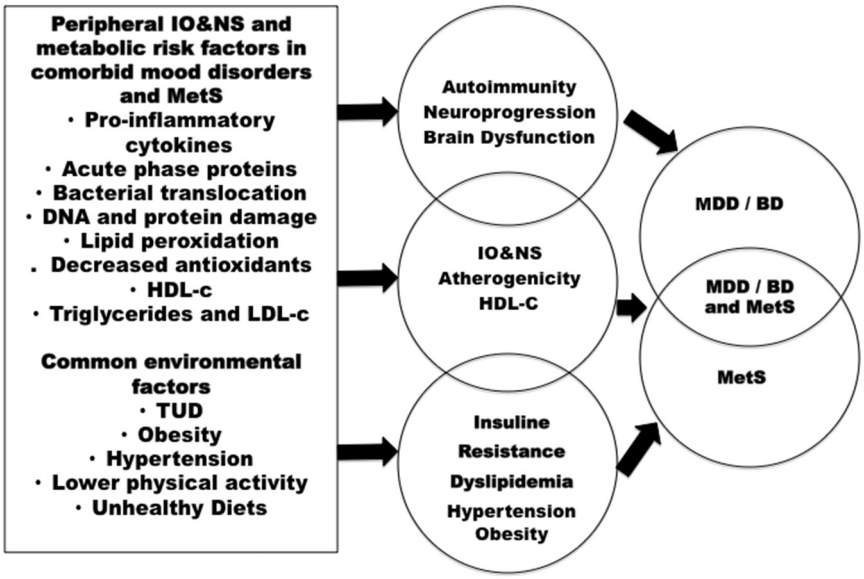

Fig. 2. Relationship between IO & NS and metabolism that contribute to BD and MDD.

preventing or reducing atherogenicity in comorbid MetS and mood disorders. For example, statins used to prevent heart disease by reducing cholesterol, also reduce inflammation and protect against oxidative damage, with potential as MDD treatment (Gougol et al., 2015; Redlich et al., 2014), while antidepressants have anti-IO & NS effects (Maes et al., 2012).

Fig. 3 shows new possible add-on treatments of comorbid MetS and MDD/BD and of increased atherogenicity in MDD/BD. This figure and following discussion are based on those of a previous paper reviewing new drug targets in depression, e.g. inflammatory pathways, immune pathways, oxidative pathways and lowered antioxidant levels (Maes et al., 2012). In addition to immune-inflammatory targeted treatments (e.g. acetylsalicylic acid, statins, cyclooxygenase-2 (COX-2) inhibitors, omega-3 polyunsaturated fatty acids, etc) and antioxidant treatments, such as N-Acetyl cysteine (NAC) also lifestyle interventions (e.g. diets and physical activities) may serve as adjunctive treatment in comorbid MetS and MDD/BD.

A first possible add on treatment for comordid mood disorders and MetS targeting inflammatory and oxidative pathways is curcumin, a food additive commonly used in Indian culinary, which has an antidepressive effect by modulating IO & NS pathways and neuroprogression as well (Kulkarni et al., 2009). Curcumin also inhibits the cyclooxygenase-2 (COX-2) isoenzyme, transcription of NF-κB and blocks the synthesis of inducible nitric oxide synthase (iNOS) enzyme (Song and Wang, 2011). The antioxidant effects of curcumin have been shown to attenuate adriamycin-induced cardiotoxicity (Venkatesan, 1998) and prevent diabetic cardiovascular complications (Ghosh et al., 2015). Futhermore, curcumin can protect against the pathological changes seen in atherosclerosis (Wongcharoen and Phrommintikul, 2009) by decreasing serum cholesterol levels and by its anti-thrombotic (Srivastava et al., 1985), anti-proliferative (Huang et al., 1992), and anti-inflammatory (Jurenka, 2009) effects.

Resveratrol, another strong antioxidant and polyphenol, exerts antidepressant-like effects in rats exposed to chronic unpredictable mild stress (Liu et al., 2016). These antidepressant effects can in part be explained by its antioxidant actions and up-regulation of the phosphor-Akt and mTOR pathway in the hippocampus (Liu et al., 2016). Resveratrol exhibits cardioprotective properties, which involve antioxidant and anti-inflammatory effects by targeting AMP-activated protein kinase (AMPK), SIRT1 and NO (Kuno et al., 2015; Raj et al., 2015). Resveratrol also has antihypertensive effects and can decrease plasma triglyceride and LDL-c levels, while increasing HDL-c (Bonnefont-Rousselot, 2016).

Accumulating pre-clinical evidence provides support for the concept

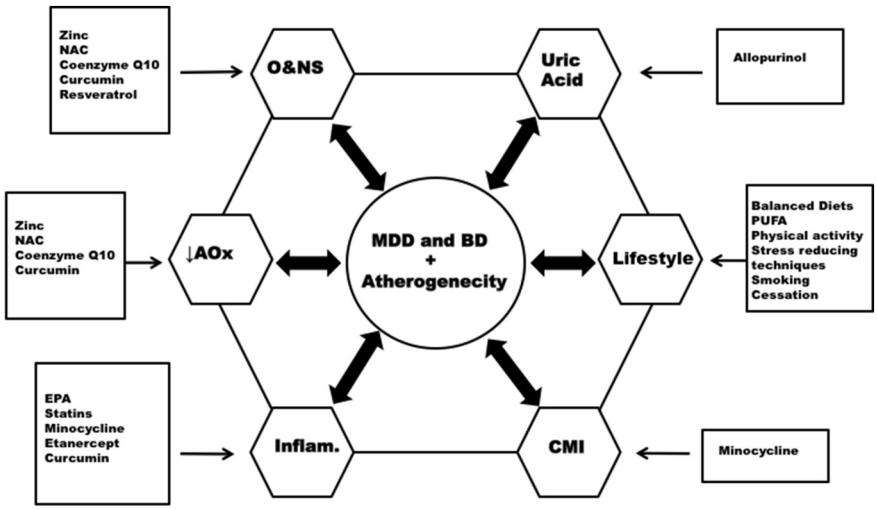

Fig. 3. New drug targets to treat comorbid MetS and MDD/BD. Possible adjunctive treatments targeting anti-inflammatory, antioxidant and oxidative pathways.

that TNF-α inhibition may alleviate depressive-like behavior (Bortolato et al., 2015) and exert pro-cognitive effects (Raftery et al., 2012). TNF-α antagonism has a cardioprotective effect by alleviating myocardial ischemia-reperfusion injury via downregulation of adiponectin in animals and partly via Notch1 signaling-mediated promoting suppression of IO & NS pathways (Gao et al., 2015; Pei et al., 2015). Etanercept, a TNF-α antagonist, reduces the cardiovascular risk in patients with psoriatic arthritis (Di Minno et al., 2016). Etanercept decreases microglial activation and prevent neuronal damage in animal models of ischemic and traumatic brain injury (Tuttolomondo et al., 2014).

Minocycline, an anti-inflammatory tetracycline derivative, has antidepressant-like effects in rats as shown by positive forced swimming test (Molina-Hernandez et al., 2008). Minocycline exerts very promising neuroprotective effects such as inhibition of microglial activity, glutamate toxicity and caspase 1-dependent apoptosis produced by ischemic insults (Kikuchi et al., 2012; Liao et al., 2013). In rats, after cardiac arrest and cardiopulmonary resuscitation, administration of minocycline significantly decreases microglial responses, TNF-α levels and neuronal death (Wang et al., 2015). The administration of minocycline significantly reduces the expression of extracellular matrix metalloproteinase inducer (CD147) and matrix metalloproteinase (MMP)-9 and enhances stability of atherosclerotic plaques in animal models having an equally effect as Atorvastatin (Gao et al., 2013).

Eicosapentaenoic acid (EPA), one of the ω3 PUFAs, has a significant antidepressant activity (Lin and Su, 2007), probably due to suppression of pro-inflammatory products and Th-1-like cytokines and enhancing neurogenesis (Song and Wang, 2011). Many studies have indicated that ω3 PUFA consumption may lower cardiovascular risk (Kakoti et al., 2015). The suggested mechanisms associated with the benefits of ω3 PUFAs are stabilization of plaque formation, normalizing blood pressure, and anti-inflammatory properties (Chaddha and Eagle, 2015; Kakoti et al., 2015). Furthermore, ω3 PUFAs lower triglyceride levels and may increase HDL-c levels (Chaddha and Eagle, 2015).

Coenzyme Q10 has important anti-IO & NS properties via the suppression of NF-κB and through the modulation of the transcription of genes governing the pro-inflammatory JAK/STAT pathway (Bortolato et al., 2016a,b). In rats, treatment with coenzyme Q10 has antidepressant activity in part by maintaining mitochondrial function and its well documented antioxidant properties (Aboul-Fotouh, 2013). Coenzyme Q10 may be recommended to patients at risk for cardiovascular disease as an adjunct to conventional treatment (Yang et al., 2015). Coenzyme Q10 can help prevent the development of endothelial dysfunction by preventing IO & NS, for example in hypertension patients with lowered coenzyme Q10 levels (Gao et al., 2011; Yang et al., 2015). Moreover, in animal models, coenzyme Q10 can have antidiabetic effects showing a promising effect as dietary supplement in the management of diabetic encephalopathy (Motawi et al., 2016).

Clinical studies show a significant benefit of zinc supplementation as an antidepressant (Nowak et al., 2005). The potential antidepressant effect of zinc may be explained by anti-IO & NS activities and effects on neuroprogression, including neuroplasticity, *N*-methyl-D-aspartate (NMDA)-receptors and neurogenesis (Szewczyk et al., 2011). Inadequate zinc nutritional status has been associated with an increase in risk for coronary heart disease (Lee et al., 2015). This could be explained by effects on acute redox stress in cardiomyocytes and prevention of inflammatory processes triggered during myocardial damage (Lee et al., 2015). A systematic review showed that lowered zinc is associated with increased cardiovascular risk in 6 case-control studies but not in 2 cohort studies (Hashemian et al., 2015).

N-Acetylcysteine (NAC) has been successfully used in the management of BD and MDD patients (Berk et al., 2013; Deepmala et al., 2015; Fernandes et al., 2016). Interestingly, NAC has been shown to have a significant impact on blood pressure in patients with type 2 diabetes (Goszcz et al., 2015; Martina et al., 2008). NAC also reduces platelet–monocyte interactions, a marker and potential mediator of cardiovascular disease, in patients with type 2 diabetes (Goszcz et al., 2015; Treweeke et al., 2012). Intravenous infusion of NAC during thrombolysis was associated with a decrease in infarct size and better preservation of left ventricular function and reduction of thrombotic propensity. Therefore, it was concluded that NAC might be an alternative therapy to aspirin in type-2 diabetes patients (Gibson et al., 2011; Marchetti et al., 1999).

Allopurinol is widely used in the treatment of hyperuricemia and gout, but it is also a strong antioxidant by inhibiting xanthine oxidase, which catalyzes the conversion of hypoxanthine, via xanthine, to uric acid (Goszcz et al., 2015). Importantly, studies with depression subjects have found high levels of xanthine oxidase (Herken et al., 2007). Allopurinol might have antidepressant effects by increasing serotonin due to inhibition of tryptophan 2,3-dioxygenase (Becking and Johnson, 1967; Gurbuz Ozgur et al., 2015; Karve et al., 2013). Allopurinol also has been used in acute mania showing benefits as adjuvant therapy but not as monotherapy (Akhondzadeh et al., 2006; Jahangard et al., 2014; Machado-Vieira et al., 2008; Weiser et al., 2014). Allopurinol has been studied as a potential adjunct therapy for cardiovascular disease in preclinical studies showing a decrease in mortality and increase in left ventricular function in animal models of heart failure (Naumova et al., 2005; Stull et al., 2004). However, randomized clinical trials have failed to replicate these beneficial findings (Givertz et al., 2015; Nasr and Maurice, 2010).

Statins have been used as an important drug in the treatment of atherosclerosis (Bragg and Walling, 2015; Menon et al., 2015). A recent meta-analysis suggests that statins could be useful as an adjunctive treatment of depressive symptoms (Kohler et al., 2016; Salagre et al., 2016). The antidepressive effect of simvastatin may be explained by targeting neurotransmitters, such as dopamine, IO & NS pathways including the TRYCATs pathway and NMDA receptor activity (Mabuchi et al., 2007b). However, simvastatin could reduce levels of coenzyme Q10 by around 40% showing the importance of medical interactions in the treatment of mood disorders (Anderson and Maes, 2014; Mabuchi et al., 2007a).

8. Conclusions

Mood disorders and the MetS show a high degree of comorbidity, which is closely related to activated IO & NS pathways, increased atherogenicity (increased AIP, Castelli indices) and lower levels of endogenous anti-inflammatory agents and antioxidants. Given the IO & NS and metabolic dysregulations both peripherally and centrally, BD and MDD may be viewed as systemic disorders including metabolism and brain. Measuring these IO & NS and metabolic biomarkers may be useful to delineate MDD/BD patients at risk for comorbid CVD. Moreover, these pathways may be targeted to treat and prevent MDD/BD comorbid with MetS. We review new treatments, e.g. drugs and antioxidant supplements and lifestyle modifications, which may be used to target those pathways.

List of abbreviations

BD	Bipolar Disorder
MDD	Major Depressive Disorder
BMI	Body Mass Index
HOMA	homeostasis model assessment
HOMA2	updated homeostasis model assessment
HOMA2IR	Insulin Resistance Homeostasis Model Assessment
HOMA2S%	insulin sensitivity homeostasis model assessment
HOMA2B%	beta-cell function homeostasis model assessment
NLR	Nucleotide-binding oligomerization domain (Nod)-Like Receptors
NLRP3	Nod-Like Receptors pyrin domain containing 3
CFH	complement factor H
DNA	Deoxyribonucleid acid
NF-κB	nuclear factor-kappa B

GSH	glutathione
PUFAs	polyunsaturated fatty acids
PPAR	peroxisome proliferator activate receptors
SIRTs	Sirtuins
SIRT1	Silent information regulator T1
COX-2 inhibitors	cyclooxygenase-2
5-HTT	*STIn2VNTR* polymorphism of the serotonin transporter
AMPK	AMP-activated protein kinase
NMDA	*N*-methyl-D-aspartate
IO & NS	Oxidative And Nitrosative Stress
AIP	Atherogenic Index Of Plasma
HDL-c	High-Density Lipoprotein Cholesterol
LDL-c	low density lipoprotein cholesterol
OxLDL	serum oxidized LDL
BDNF	Brain-Derived Neurotropic Factor
IDF	International Diabetes Foundation
HPA	Hypothalamic–Pituitary–Adrenal Axis
PICs	Pro-Inflammatory Cytokines
TNF-α	Tumor Necrosis Factor-Alpha
IL-6	Interleukin-6
IL-6R	Interleukin 6 Receptor
IL-1β	Interleukin-1 Beta
IL-18	Interleukin-18
CRP	C-Reactive Protein
TRYCAT	Tryptophan Catabolites
O & NS	Oxidative and Nitrosative Stress
Mets	Metabolic Syndrome
MeSH	Medical Subject Headings
CNS	Central Nervous System
IFN-γ	Interferon-Gamma
TGF-H1	Transforming Growth Factor Beta-1
IL-1Ra	IL-1 Receptor Antagonist
G-CSF	Granulocyte Colony-Stimulating Factor
Stnfr1	Soluble TNF Receptor-1
Stnfr2	Soluble TNF Receptor-2
CXCL10	C-X-C motif cytokine ligand 10
CREB	Calcium/Cyclic AMP Responsive-Element-Binding Protein
IDO	Indoleamine 2,3-Dioxygenase
TDO	Tryptophan 2,3-Dioxygenase
MAPK	Mitogen Activated Protein Kinases
RNS	Reactive Nitrogen Species
ROS	Reactive Oxygen Species
SOD	Superoxide Dismutase
CAT	Catalase
PFC	Prefrontal Cortex
TBARS	Thiobarbituric Acidic Reactive Substances
NO	Nitric Oxide
NOx	nitric oxide by-products
iNOS	inducible nitric oxide synthase
Gpx	Glutathione Peroxidase
GST	Glutathione S-Transferases
MDA	Malonylaldehyde
AOPP	Advanced Oxidation Protein Products
TRAP	Total Radical Trapping Antioxidant Parameter
MLNs	Mesenteric Lymph Nodes
LPS	Lipopolysaccharides
PRR	Pattern Recognition Receptors
TLR	Toll-Like Receptor
TLR4	Toll-Like Receptor 4
PAMP	Pathogen-Associated Molecular Patterns
DAMP	Damage-Associated Molecular Patterns
CVD	Cardiovascular Disease
ATP III	Adult Treatment Panel III Report
T2DM	Diabetes Mellitus Type 2
NAC	*N*-acetylcysteine
TUD	Tobacco Use Disorder
PON1	Paraoxonase 1
GSTT1	Glutathione-*S*-Transferase Theta-1
GSTM1	Glutathione-*S*-Transferase M-1

Conflict of interest

The authors have no conflict of interest with any commercial or other association in connection with the submitted article.

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