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Review article

Common biological mechanisms between bipolar disorder and type 2 diabetes: Focus on inflammation

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ABSTRACT

Introduction: Bipolar disorder (BD) patients present a 3–5 fold greater risk of developing type 2 diabetes (T2D) compared to general population. The underlying mechanisms for the increased prevalence of T2D in BD population are poorly understood.
Objectives: The purpose of this review is to critically review evidence suggesting that inflammation may have an important role in the development of both BD and T2D.
Results: The literature covered in this review suggests that inflammatory dysregulation take place among many BD patients. Such dysregulated and low grade chronic inflammatory process may also increase the prevalence of T2D in BD population. Current evidence supports the hypothesis of dysregulated inflammatory processes as a critical upstream event in BD as well as in T2D.
Conclusions: Inflammation may be a factor for the development of T2D in BD population. The identification of inflammatory markers common to these two medical conditions will enable researchers and clinicians to better understand the etiology of BD and develop treatments that simultaneously target all aspects of this multi-system condition.

Contents

Abbreviations: ACE, angiotensin converting enzyme; AGEs and RAGE, advanced glycation products (AGEs) and receptor for AGEs; BCL2A1, B-cell lymphoma 2A1; BD, bipolar disorder; BMI, body mass index; C3, C4 and C6, complement factors 3, 4 and 6; CCL2, chemokine ligand 2; CCL11, ligand 11; CCR-2, chemokine receptor-2; COX-1 and COX-2, cyclooxygenase-1 and cyclooxygenase-2; CRP, C-reactive protein; DPP-4, dipeptidyl peptidase-4; EMP1, epithelial membrane protein 1; FSTL1, follistatin-like 1 cytokine; GFAP, glial fibrillary acidic protein; GM-CSF, granulocyte monocyte-colony stimulating factor; Hb_{A1C}, glycosylated hemoglobin; IFNα, interferon alpha-isoform; IFNγ, interferon gamma-isoform; IKKβ, kinase of the IKK family, phosphorylates inhibitors of NF-kappa-B; IKKβ, kinase of the IKK family, phosphorylates inhibitors of NF-kappa-B; IL-1, interleukin-1; IL-1β, interleukin-1 β-isoform; JNK, c-Jun N-terminal kinase; MAPK-6, mitogen-activated protein kinase 6; NF-κB, nuclear factor-kappa B; NLRP3 inflammasome, NAIP, CIITA, HET-E, TP-1 (NACHT), leucine rich repeats (LRR) and pyrin (PYD) domains-containing protein 3; NSAIDs, nonsteroidal anti-inflammatory drugs; PAI-1, plasminogen activator inhibitor-1; PGE2, prostaglandin E2; PLA_2, phospholipase A2; PPARγ-R, peroxisome proliferator-activated receptor gamma; PTX3, pentraxin 3; PUFA, polyunsaturated fatty acids; sIL-2R, soluble interleukin-2 receptor; sIL-6R, soluble interleukin-6 receptor; T2D, type 2 diabetes; TCF7L2, transcription factor 7-like 2; TGF-β, transforming growth factor β-isoform; TLR-4, toll-like receptor 4; TLR-2, toll-like receptor 2; TNF-α, tumor necrosis factor α-isoform; sTNFR1, soluble tumor necrosis factor receptor 1; VEGF, vascular endothelial growth factor.

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1. Introduction

Bipolar disorder (BD) and type 2 diabetes (T2D) are two highly disabling and apparently unrelated human disorders. However, both conditions share high comorbidity (Cassidy et al., 1999; Regenold et al., 2002; Ruzickova et al., 2003) as BD patients are at 3–5 times higher risk of developing T2D than general population (Calkin et al., 2013; Cassidy et al., 1999; Lilliker, 1980; Regenold et al., 2002). BD is conceptualized as a multi-system disorder with manic-depressive symptoms, cognitive impairment, and structural/functional brain abnormalities (Coffman et al., 1990; Swayze et al., 1990) coupled with increased risk for disturbances in glucose homeostasis, insulin resistance, higher body mass index and abnormal lipid profile with cognitive, autonomic, and sleep disturbances (for reviews, see: Calkin et al., 2013; Leboyer et al., 2012; Teixeira et al., 2013). Additionally, treatments of BD patients with mood stabilizers like lithium and valproic acid can exacerbate risk factors for T2D such as weight gain and craving for fast food fats (Chengappa et al., 2002; Dinesen et al., 1984; Martin et al., 2009). Evidences also support that, among BD patients, the comorbidity with metabolic disorders like T2D is associated with increased frequency of episodes, hospitalizations, severity of illness and suicidality as well as poor response to mood stabilizers (B. Kim et al., 2009; Calkin et al., 2009; Chengappa et al., 2002; Dinesen et al., 1984; Gomes et al., 2010; Martin et al., 2009; Ruzickova et al., 2003), as well as accelerated brain aging (Fotuhi et al., 2012).

Based on this evidence, several pathophysiological mechanisms involved in the development of BD have been proposed (Belmaker and Agam, 2005; Cousins et al., 2009; Fornito et al., 2009). However, there is no definitive understanding with regard to the biological basis of BD origin and progression. Thus, diagnosis of BD still heavily relies on traditional methods like behavioral observations, patient questionnaire and family reports.

In contrast, T2D has hallmark clinical features such as hyperglycemia that is routinely tested in laboratories for diagnosis and disease management (Lindmark et al., 2006; Manickam et al., 2013). T2D is a heterogeneous disorder that was previously referred to as 'mature onset' or 'non-insulin dependent diabetes mellitus (NIDDM)' and represents about 90% of global diabetes patients. It is a by-product of interactions between genetic susceptibility and environmental factors with characteristic decrease in response to insulin by target tissues — also called as insulin resistance. Considering the high rates of comorbidity between BD and T2D and the associated financial, emotional and healthcare burden on patients and family, there is an immediate need to search for common biological foundations for their co-existence. Some shared postulations among BD and T2D pathology are: genetic alterations (Kawamoto et al., 2004; Ross, 2011), elevated stress response and allostatic overload (i.e. inefficient homeostatic response) (Brietzke et al., 2011), neurochemical alterations (Hajek et al., 2013), lifestyle (Calkin et al., 2013; Morriss and Mohammed, 2005), BD medications (Castilla-Puentes, 2007), inflammation (Donath and Shoelson, 2011) and oxidative stress (de Sousa et al., 2014; Gohel and Chacko, 2013). This review aims at highlighting the importance of BD and T2D comorbidity and postulates 'inflammation' as a common malefactor for their coexistence.

2. Inflammation in bipolar disorder and type 2 diabetes

2.1. Inflammation and bipolar disorder

Balanced and acute inflammatory response is an evolutionary conserved and protective mechanism of the mammalian body to defend against various insults like stress, injury or infection and to clear localized deposition of unwanted metabolites and dead/damaged cells. However, inflammation as a body's protective response can go awry accompanied by constellation of pathologies if it has to fight for an extended periods as in chronic inflammatory conditions. As discussed in detail below, dysregulated and low grade chronic inflammatory responses are among the most consistently observed findings in BD patients (Goldstein et al., 2009; Kapczinski et al., 2011; Padmos et al., 2008).

Immune cells-derived cytokines are the major components involved in regulation of inflammatory processes. Cytokines are gaining widespread acknowledgement for their potential utility as prognostic and diagnostic markers in diverse human ailments (Dinarello et al., 2010). Multiple lines of evidence from clinical (Brietzke et al., 2009; Cunha et al., 2008; Dickerson et al., 2007), in vitro (Kim et al., 2007; Knijff et al., 2007) and genetic findings (Drexhage et al., 2010a; Padmos et al., 2008) also point to changes in cytokine levels in BD (Table 1). Based on their physiological properties, individual cytokines can be classified as anti-inflammatory (ex. IL-4, 10, 13, IFNα and TGF-β) and pro-inflammatory (ex. IL-1β, IL-2, 6, 8, 12, 18, TNF-α, IFNγ, VEGF and GM-CSF) in nature. Hypothetically, pro-inflammatory cytokines worsen the disease outcome, whereas anti-inflammatory cytokines work as counteractive mechanisms against pro-inflammatory responses. Additionally, immune system produces natural antagonists to neutralize pro-inflammatory cytokines mediated biological responses (Drexhage et al., 2010b). Cytokines require solubilized or cell surface receptors to exert their physiological and/or pathophysiological effects. Inflammatory cytokines could potentially activate neuronal apoptotic pathways, decrease serum neurotrophins levels and neuronal repair with changes in mood states as in BD. A significant progress has been made in recent past characterizing mood specific alterations in inflammatory markers in BD population. In general, meta-analysis demonstrated consistently elevated sIL-2R, sIL-6R, TNF-α, sTNFR1, IL-4 and no differences in IL-6, IL-1β, IL-1RA, IL-8, sTNFR2, IL-5, IL-10 and IFNγ during mania when compared with healthy control participants (Munkholm et al., 2013). Further, pro-inflammatory cytokines like IL-6, IL-8, CRP, and TNF-α seem to be elevated during depressive episodes (Brietzke et al., 2009; O'Brien et al., 2006; Ortiz-Dominguez et al., 2007), IL-2, sIL-2R, IL-4, IL-6, IL-8, TNF-α, and sTNFR1 during manic episodes (Barbosa et al., 2011; Brietzke et al., 2009; Hope et al., 2011; Kim et al., 2007; Maes et al., 1995; O'Brien et al., 2006; Ortiz-Dominguez et al., 2007; Tsai et al., 2001), and IL-4 and sTNFR1 (Barbosa et al., 2011; Tsai et al., 2012) during euthymia in BD patients (Brietzke et al., 2009) compared to healthy controls.

Production of pro- and anti-inflammatory cytokines by inflammatory cells is influenced by prostaglandins and leukotrienes derived from polyunsaturated fatty acid (PUFA) like arachidonic acid. Membrane phospholipids release arachidonic acid in response to triggers like tissue damage which is catalyzed by enzyme phospholipase A2 (PLA_2). This