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IDO chronic immune activation and tryptophan metabolic pathway: A potential pathophysiological link between depression and obesity

Adriano José Maia Chaves Filho[a,b], Camila Nayane Carvalho Lima[a,b], Silvânia Maria Mendes Vasconcelos[a,b], David Freitas de Lucena[a,b], Michael Maes[c,d,e], Danielle Macedo[a,b,*]

[a] Neuropsychopharmacology Laboratory, Drug Research and Development Center, Faculty of Medicine, Universidade Federal do Ceará, Fortaleza, CE, Brazil
[b] Department of Physiology and Pharmacology, Faculty of Medicine, Universidade Federal do Ceará, Fortaleza, CE, Brazil
[c] Impact Strategic Research Center, Deakin University, Geelong, Australia
[d] Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
[e] Health Sciences Graduate Program, Health Sciences Center, State University of Londrina, Londrina, Brazil

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ABSTRACT

Obesity and depression are among the most pressing health problems in the contemporary world. Obesity and depression share a bidirectional relationship, whereby each condition increases the risk of the other. By inference, shared pathways may underpin the comorbidity between obesity and depression. Activation of cell-mediated immunity (CMI) is a key factor in the pathophysiology of depression. CMI cytokines, including IFN-γ, TNFα and IL-1β, induce the catabolism of tryptophan (TRY) by stimulating indoleamine 2,3-dioxygenase (IDO) resulting in the synthesis of kynurenine (KYN) and other tryptophan catabolites (TRYCATs). In the CNS, TRYCATs have been related to oxidative damage, inflammation, mitochondrial dysfunction, cytotoxicity, excitotoxicity, neurotoxicity and lowered neuroplasticity. The pathophysiology of obesity is also associated with a state of aberrant inflammation that activates aryl hydrocarbon receptor (AHR), a pathway involved in the detection of intracellular or environmental changes as well as with increases in the production of TRYCATs, being KYN an agonists of AHR. Both AHR and TRYCATS are involved in obesity and related metabolic disorders. These changes in the TRYCAT pathway may contribute to the onset of neuropsychiatric symptoms in obesity. This paper reviews the role of immune activation, IDO stimulation and increased TRYCAT production in the pathophysiology of depression and obesity. Here we suggest that increased synthesis of detrimental TRYCATs is implicated in comorbid obesity and depression and is a new drug target to treat both diseases.

1. Introduction

Obesity and depression are two of the most pressing and costly health problems faced today. Several studies indicate that the prevalence of obesity has increased alarmingly in recent decades. For example, from 1980 to 2008, the overall prevalence of obesity has more than doubled, with 10% of men and 14% of women around the world being considered obese (i.e., body mass index > 30) (Preiss et al., 2013; Schneider et al., 2010). These data have a serious impact since obesity is a major risk factor associated with chronic diseases such as hypertension, coronary artery disease, type 2 diabetes mellitus and cancer, as well as with the increased risk of premature death (Fontaine et al., 1997; Hrabosky and Thomas, 2008; Allison et al., 2009).

Depression, in turn, is the leading cause of disability worldwide

Abbreviations: 1-MT, 1-methyltryptophan; 3-HK, 3-hydroxykynurenine; 5-HT, serotonin; 5-HTP, 5-hydroxy-L-tryptophan; 5-HIAA, 5-hydroxyindoleatic acid; ACTH, adrenocorticotrophic hormone; AADC, aromatic L-amino acid descarboxylase; AA-NAT, aralkylamine *N*-acetyltransferase; AHR, aryl hydrocarbon receptor; AM, autobiographical memory; BMI, body mass index; BCG, bacille Calmette–Guérin; BDNF, brain derived neurotrophic factor; CNS, central nervous system; COX-2, cyclooxygenase-2; CRP, C-reactive protein; fMRI, functional magnetic resonance imaging; HIOMT, hydroxyindole *O*-methyltransferase; HFD, high fat diet; HPA, hypothalamic-pituitary-adrenal axis; IDO, indoleamine 2,3-dioxygenase; IFN, interferon; IL, interleukin; LPS, lipopolysaccharide; KAT, kynurenine aminotransferase; KMO, kynurenine 3-monooxigenase; KYN, kynurenine; KYNA, kynurenic acid; MDD, major depressive disorder; MRL, medial temporal lobe; MT2, melatonergic receptor 2; NAD, nicotinamide adenine dinucleotide; NAS, *N*-acetylserotonin; NFκB, nuclear factor κB; NMNAT, nicotinamide mononucleotide adenyltransferase; NOS, nitric oxide synthase; QUIN, quinolic acid; QPRT, quinolinate phosphoribosyltransferase; SNP, single nucleotide polymorphism; TDO, tryptophan 2,3-dioxygenase; TNF, tumor necrosis factor; TRYCATs, tryptophan catabolites

* Corresponding author at: Drug Research and Development Center, Department of Physiology and Pharmacology, Federal University of Ceará, Rua Cel. Nunes de Melo 1000, 60430-270 Fortaleza, CE, Brazil.
E-mail address: danielle.macedo@ufc.br (D. Macedo).

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being the major contributor to the overall global burden of disease. Recently, the World Health Organization (WHO) recognizes depression as the main cause of disability and loss of productive life years worldwide (WHO, 2015; Kessler et al., 2015). In the USA 2013, it was estimated that > 15.7 million people had episodes of major depression, accounting for > 6.6% of adult population of this country (Substance Abuse and Mental Health Services Administration, 2014). In addition, similarly to obesity, depression has been associated with increased risk of developing severe chronic diseases such as atherosclerotic heart disease, type 2 diabetes mellitus and cancer and increased mortality rates (Clarke and Currie, 2009; Grippo, 2009; Preiss et al., 2013).

An increasing body of evidence has pointed to an important bi-directional link between obesity and depression (Miller et al., 2003; Rosmond, 2004; Hryhorczuk et al., 2013; Castanon et al., 2015). In this context, population-based analysis revealed that obese people have an increased incidence of depressive symptoms (> 30%) compared to healthy subjects (Pan et al., 2012; Lin et al., 2013). Furthermore, longitudinal studies have demonstrated a prospective link between obesity and depression with obese individuals having a higher risk for developing depression (about 55%) over time. Conversely, individuals with depression present a higher risk to become obese (about 58%) (Lupp et al., 2007; Preiss et al., 2013). There is also a significant association between obesity and the onset of mood changes and cognitive deficits in older adults (Cournot et al., 2006; Roberts et al., 2010; Dahl et al., 2013). Of note, depression significantly impacts the quality of life and social skills of obese people. Depression also impairs adherence to treatment and beneficial changes in lifestyle, representing an additional risk factor for the worsening of obesity and its pathological complications, particularly cardiovascular disease (Roberts et al., 2003; Simon et al., 2006; Zhao et al., 2011; Hamer et al., 2012).

1.1. Neurobiology of depression: an overview

For many years, since the introduction of the first antidepressants, the pathophysiology of depression was restricted to a deficit in biogenic amines (López-Muñoz et al., 2007; López-Muñoz and Alamo, 2009). In this regard, the promising antidepressant effects of the class of antidepressant drugs called serotonin (5-HT) uptake inhibitors gave rise to the development of the so-called serotonin hypothesis of depression. Based on this hypothesis depression was primarily associated with a decrease in 5-HT synthesis and action on its receptors (Fangmann et al., 2008; López-Muñoz and Alamo, 2009). Nevertheless, although drugs with mechanism of action based on the serotonergic theory of depression have shown efficacy in the treatment of a subgroup of individuals, its pharmacological potential is currently limited. This is due to the fact that a large population of patients seems to be refractory or to have a late onset of action when prescribed these drugs. Thus, the monoaminergic theory of depression, as proposed, presents some limitations. Modern theories are proposed to better explain the pathophysiology of this mental disorder (Maes et al., 2011b; Salazar et al., 2012; Réus et al., 2015). Activated immune-inflammatory pathways are associated with depression and may be induced by common trigger factors of depression, including psychosocial stressors, exogenous stressors and medical comorbidities (Maes et al., 2011a, 2011b). Indeed, physical and psychological stressors can activate the immune system in both the periphery and Central Nervous System (CNS) thereby releasing inflammatory cytokines leading to neurotransmitter and behavioral changes (Maier and Watkins, 1998, Koo and Duman, 2008).

In fact, high levels of pro-inflammatory cytokines, such as interferon (IFN)-γ, tumor necrosis factor (TNF)-α, and interleukin (IL)-1β have been consistently reported in plasma and brain samples of depressive patients (Maes, 1995a, 1995b; Kling et al., 2007; Song et al., 2009; Dowlati et al., 2010; Felger and Lotrich, 2013). This is reinforced by the findings that in humans and animal models a pro-inflammatory state induced by exogenous cytokines, including IL-6 (Sukoff Rizzo et al., 2012; Kong et al., 2015), TNFα (Reichenberg et al., 2001; Simen et al., 2006), IFN-α (Raison et al., 2005, 2013) and bacterial endotoxins or lipopolysaccharides (LPS) (Grigoleit et al., 2011; Custódio et al., 2013;Tomaz et al., 2014) may cause depression and depression-like symptoms, such as lethargy, anhedonia, anorexia, decreased sexual activity and sleeping disorders. Therefore, it is now considered that neuro-immune mechanisms play a key role in the pathogenesis and pathophysiology of depression (Maes, 1995a, 1995b; Schiepers et al., 2005; Maes et al., 2011b; Rosenblat et al., 2014).

1.2. Pathophysiology of obesity: an overview

Obesity is not only a metabolic disease, but also a chronic inflammatory condition, in which both innate and acquired immune responses are affected (Dandona et al., 2004; Bastard et al., 2006; Cancello and Clément, 2006). Elevated serum levels of inflammatory markers e.g. IL-1β, TNFα and IL-6 have been observed in obese patients (Kopp et al., 2005; Park et al., 2005; Capuron et al., 2011a) and in animal models of obesity (Bigorgne et al., 2008; Cani et al., 2009; Pistell et al., 2010; Lawrence et al., 2012; Dinel et al., 2014b). Aberrant inflammation activates aryl hydrocarbon receptor (AHR), a pathway involved in the detection of intracellular or environmental changes, sensing light, oxygen and redox potential (Gu et al., 2000). Thus, based on the fact that genetic contribution to obesity is estimated by 25–70%, while environmental factors (consumption of the high-calorie, high-fat, low-fiber Western diet) contribute by 30–75% (Baillie-Hamilton, 2002), AHR seems to be the biological entity that tightly links genes and the environment in the pathophysiology of obesity (Moyer et al., 2016).

Interestingly, a significant association between systemic pro-inflammatory status and the emergence of depressive symptoms (Capuron et al., 2008; Castanon et al., 2014) and cognitive deficits (Sweat et al., 2008; Sellbom and Gunstad, 2012) has been observed in obese individuals. In addition, an important elevation of pro-inflammatory cytokines is found in brain areas associated with mood disorders, such as the hippocampus and hypothalamus, in experimental obesity (Pistell et al., 2010; André et al., 2014; Miller and Spencer, 2014). Of note, these findings were positively associated with the onset of anxiogenic and depressive-like behaviors (Pistell et al., 2010; André et al., 2014; Dinel et al., 2014).

1.3. An overview of the pro-inflammatory state in depression and obesity and tryptophan catabolites (TRYCATs) pathway

The overproduction of pro-inflammatory cytokines may activate a major enzyme involved in tryptophan (TRY) metabolism, namely indoleamine 2,3-dioxygenase (IDO), taking away TRY from 5-HT synthesis thereby driving the production of tryptophan catabolites (TRYCATs), including kynurenine (KYN), 3-hydroxykynurenine (3-HK), kynurenic acid (KYNA), xanthurenic acid, quinolinic acid (QUIN), picolinic acid and anthranilic acid (Connor et al., 2008; Maes et al., 2008; Maes, 2011; Dinel et al., 2014; Réus et al., 2015). These TRYCATs have different biological and neurobehavioral actions. For example, KYNA in physiological levels seems to present antioxidant and neuroprotective properties mainly based on its ability to bock *N*-methyl-D-aspartate (NMDA) receptors. On the other hand, 3-HK and QUIN have noxious effects including neurotoxic, excitotoxic, cytotoxic and pro-oxidative effects (Guillemin et al., 2001; Maes et al., 2007, 2011).

There is some evidence that depression may be associated with an increased production of TRYCATs, especially the detrimental ones (Steiner et al., 2011). Previous studies have demonstrated that animals subjected to chronic stress or immune challenge with lipopolysaccharide (LPS), two well-established animal models of depression, present increases in IDO expression/activity and levels of detrimental TRYCATs (KYN, 3-HK, QUIN) in brain areas related to mood regulation, such as the hippocampus, hypothalamus and amygdala (Connor et al., 2008; O'Connor et al., 2009a; O'Connor et al., 2009b; Laugeray et al., 2010). In addition, some authors reported significant associations