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

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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 , TNF α and IL-1 β , 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-hydroxyindoleacetic acid; ACTH, adrenocorticotrophic hormone; AADC, aromatic L-amino acid decarboxylase; 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-monooxygenase; KYN, kynurenine; KYNA, kynurenic acid; MDD, major depressive disorder; MRL, medial temporal lobe; MT2, melatonin receptor 2; NAD, nicotinamide adenine dinucleotide; NAS, N-acetylserotonin; NFkB, nuclear factor kB; NMNAT, nicotinamide mononucleotide adenylyltransferase; NOS, nitric oxide synthase; QUIN, quinolinic acid; QPRT, quinolinate phosphoribosyltransferase; SNP, single nucleotide polymorphism; TDO, tryptophan 2,3-dioxygenase; TNF, tumor necrosis factor; TRYCATs, tryptophan catabolites

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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 bidirectional 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)-1 β 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), TNF α (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; Canello and Clément, 2006). Elevated serum levels of inflammatory markers e.g. IL-1 β , TNF α 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 block 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

between IDO activation or increased serum TRYCATs and the onset and severity of mood symptoms in depressive patients (Maes et al., 2002; Wichers et al., 2005; Mackay et al., 2009; Vignau et al., 2009; Gabbay et al., 2010; Meier et al., 2016; Savitz et al., 2015c).

Recently, an imbalance of TRY metabolism and increased circulating levels of detrimental TRYCATs have been reported in obese patients and related metabolic disorders, such as heart atherosclerotic disease and type 2 diabetes mellitus (Brandacher et al., 2006, 2007; Oxenkrug, 2010, 2013; Mangge et al., 2014a, 2014b; Favenne et al., 2015). Of note, KYN and less prominently KYNA, 3-HK, 3-hydroxyanthranilic acid and QUIN are endogenous AHR agonists Mezrich et al. (2010), which directly activated AHR gene expression (Sallée et al., 2014; Oxenkrug et al., 2016). Recently, a study showed that the inhibition of AHR prevents Western diet-induced obesity (Moyer et al., 2016). Furthermore, an interesting correlation has been proposed between the levels of detrimental TRYCATs and the worsening of the prognosis and pro-inflammatory status of these patients (Sulo et al., 2013; Mangge et al., 2014b; Eussen et al., 2015). Despite this evidence, it is not clear whether detrimental TRYCATs are also produced in the CNS of obese individuals or may impact the natural history of obesity including the onset of neuropsychiatric symptoms.

1.4. Aims

The objective of this paper is to review the current body of evidence that IDO activation and the resulting production of detrimental TRYCATs play a role in the pathophysiology of comorbid depression and obesity. We hypothesize that the production of detrimental TRYCATs could be a potential biological link between obesity and depression and thus a new drug target for treating comorbid obesity and depression.

2. Search strategy

A comprehensive literature search was conducted with the PubMed/MEDLINE database to identify studies that were relevant to this current review. The search terms “inflammation” [MeSH] OR “cytokines” [MeSH] OR “tryptophan” [MeSH] OR “kynurenine” [MeSH] OR “kynurenine pathway” OR “indoleamine 2,3-dioxygenase” [MeSH] OR “tryptophan 2,3-dioxygenase” OR “kynurenic acid” [MeSH] OR “quinolinic acid” [MeSH] OR “serotonin” [MeSH] OR “cognition” [MeSH] OR “cognitive functions” [MeSH] OR “melatonin” [MeSH] were cross-referenced with “Depression” [MeSH] OR “Depressive Disorder” [MeSH] OR “Depressive Disorder, Major” [MeSH] AND “Obesity” [MeSH] OR “Metabolic Syndrome” [MeSH] OR “Abdominal Fat” [MeSH]. We included papers published in English language until April 1st 2017. The inspection of reference lists of the included studies and tracking citations of included papers in Google Scholar augmented this search strategy. Observational, experimental studies in human and animal models and literature reviews addressing the role of components of the TRYCAT pathway in the pathophysiology of depression and obesity were included. The overall methodological quality of retrieved references was considered for final inclusion.

3. Results

3.1. IDO activation and increased TRY metabolism in depression

Tryptophan is an essential amino acid relevant to many physiological processes, in particular to the CNS. Tryptophan has two distinct metabolic pathways: the methoxyindole or 5-HT pathway and the oxidative or TRYCAT pathway (Fernstrom, 1983; Fernstrom and Fernstrom, 1995; Oxenkrug, 2007). The main products of methoxyindole pathway are serotonin and melatonin. Tryptophan is converted to 5-HT by the enzyme tryptophan hydroxylase being this, the rate-limiting step in the synthesis of the neurotransmitter 5-HT.

Accordingly, 5-HT levels are limiting for melatonin synthesis. On the other hand, the oxidative pathway leads ultimately to the production of nicotinamide and generation of energy through glutarate. The first step of KYN pathway is the conversion of TRY to KYN (rate-limiting step), catalyzed by two enzymes, tryptophan 2,3-dioxygenase (TDO) or IDO. Subsequently other metabolites are generated, the TRYCATs, which have important biological effects, both in the CNS and in peripheral organs (Lapin, 2003; Mackay et al., 2009; Maes et al., 2011b).

Tryptophan levels are significantly reduced in depressed patients (Joseph et al., 1984; Maes et al., 1987a, 1987b, 1990a, 1991b; Capuron et al., 2011b; Liu et al., 2015b). In these patients, TRY plasma levels may be inversely associated with severity of depression, anxiety, somatization, suicidal ideation, neuromuscular symptoms and paranoia (Lehmann, 1972; Curzon et al., 1979; Hoes et al., 1981; Joseph et al., 1984; Capuron et al., 2011b; Maes et al., 2011b; Blankfield, 2013; Flores-Ramos et al., 2014; Gostner et al., 2015; Hüfner et al., 2015). Besides this, TRY plasma levels may constitute a predictor of therapeutic response to serotonergic antidepressants, particularly selective inhibitors of the 5-HT uptake (Møller, 1985). Conversely, a favorable response to serotonergic antidepressants usually is followed by normalization of TRY levels (Møller, 1985; Healy and Leonard, 1987; Badawy and Morgan, 1991). Therefore the reduction in TRY availability in depressive patients seems to be explained by metabolic processes (Maes, 1995a,b; Maes et al., 2011b).

TDO is one of the main enzymes involved in the peripheral catabolism of TRY. This enzyme is predominantly present in the liver and some stimuli such as glucocorticoids and excessive levels of TRY can increase its activity. Generally, TDO maintains the circulating levels of TRY in homeostatic equilibrium, but may also increase the catabolism of TRY in case of increased energy demand and elevated nicotinamide synthesis (Wolf, 1974; Hoes and Sijben, 1981; Oxenkrug, 2007). Pre-clinical studies have shown that treatment with dexamethasone increases TDO activity and lowers the levels of TRY in the plasma, liver and brain, indicating that glucocorticoids induce TDO activity (Green et al., 1975; Young, 1981; Morgan and Badawy, 1989). Also dexamethasone administration to humans lowers the brain availability of TRY (Maes et al., 1990a,b,c, d).

Increased baseline hyperactivity of the hypothalamic-pituitary-adrenal axis (HPA) and the loss of the negative feedback loop of glucocorticoids, leading to increased basal serum levels of adrenocorticotrophic hormone (ACTH) and cortisol is one of the biological hallmarks of severe depression (Du and Pang, 2015; Kabia et al., 2015). Patients on prolonged use of glucocorticoids or with Cushing's syndrome, who chronically presents high levels of TDO activity, often experience neuropsychiatric disorders, such as depressive symptoms (Kelly et al., 1980, 1983). Furthermore, TRY plasma levels are negatively related to ACTH and cortisol levels in depressive patients (Maes et al. 1987a, 1990b). Therefore, it has been suggested that TDO activation in the context of HPA axis hyperactivity may be a potential contributing factor to the increased TRY catabolism and decreased bioavailability of this amino acid in depression (Maes et al., 1990a; Fukuda, 2014; Gibney et al., 2014). Another important point is that an excessive activation of HPA axis is a core alteration observed in patients suffering from psychotic depression (Belanoff et al., 2001; Keller et al., 2006). Indeed, TDO activation leads to KYNA synthesis, a NMDA receptor antagonist (Wu et al., 2013). NMDA blockade is related to the emergence of psychotic symptoms (Krystal et al., 1994).

An activated immune-inflammatory pathway is another hallmark of major depression and especially severe depression and melancholia (Maes, 1995a,b; Kling et al., 2007; Dowlati et al., 2010; Felger and Lotrich, 2013; Rosenblat et al., 2014). Originally, immunity is a homeostatic defense mechanism composed by cell (Th1-type) and humoral (Th2-type)-mediated responses. Cell-mediated immunity is that part of the immune response based on cellular interactions between T lymphocytes and monocytes through different cytokines. The first step of this response is the presentation of an antigen to T lymphocytes, like

Th (CD4⁺) and T suppressor/cytotoxic (CD8⁺) cells, and the production of cytokines, such as IFN- γ and IL-2. These cytokines, in turn, can activate monocytes/macrophages, stimulating the production of the “monocytic” cytokines, like IL-1 β , IL-6, IL-12 and TNF α , that can further activate T lymphocytes, forming a positive feedback circuit (Rocha et al., 2008; Maes, 2011). Furthermore, there is a population of T lymphocytes, designated Th3-type, which action is suppressing Th1 responses. Th3 cells primarily produce transforming growth factor beta (TGF- β) seeming to be fundamental to maintain Th1 and Th2 balance in several organs, including CNS (MyInt et al., 2005).

Additionally, in the last years, it was identified a new family of cytokines named IL-17 cytokines. This originated a new subset of Th cells, the Th17-type cells. Similar to Th1 and Th2 cells, Th17 cells require specific cytokines and transcription factors, of note, TGF- β and IL-21 for differentiation and IL-23 for growth and stabilization. While the function of this cell subtype is not completely elucidated, emerging data suggest that Th17 cells may play an important role in host defense against extracellular pathogens, which are not efficiently cleared by Th1-type and Th2-type immunity (Bettelli et al., 2007; Korn et al., 2009). Also, considerable data proposes that Th17 cytokines play highly pro-inflammatory actions and that Th17 cells mediate immune responses against self-antigens in autoimmunity disorders (Lee K et al., 2012; Sigdel et al., 2016).

In patients with depression, an abnormal exacerbation of Th1 immune responses has been repeatedly reported. In this context, previous evidence showed an increased production of IFN- γ (Maes et al., 1993, 1994; Seidel et al., 1995) and high rates of IFN- γ /IL-4 (indicative of Th-1/Th-2 balance) and IFN- γ /TGF- β (indicative of Th-1/Th-3 balance) (MyInt et al., 2005; Kim et al., 2007; Song et al., 2009) in depressed patients. Furthermore, increased levels of T-cell activation markers, such as the count of T cell CD25⁺, HLA-DR, IL-2 soluble receptor (sIL-2R); and CMI markers, including neopterin and IL-12 levels, have been demonstrated (Maes et al., 1991a, 1992; Miller et al., 2009). Therefore, a state of CMI activation marked by a mutual stimulation of T lymphocytes and monocytic cells seems to be a key factor in the inflammatory pathophysiology of depression (Maes, 1995a,b, Maes, 2011; Maes et al., 2011b).

The IDO enzyme, similarly to TDO, participates in the first step of KYN metabolic pathway. Differentially from TDO, IDO is distributed in human tissues, such as brain, lung, kidney, intestine, beyond monocytic cells, being its expression very low in physiological conditions. The inflammatory cytokine IFN- γ is the main inducer of IDO expression (Oxenkrug, 2007, 2010). Other inflammatory cytokines, such as TNF α , IL-2, IL-1 β and prostaglandin PGE₂, may also induce IDO expression, while anti-inflammatory cytokines, e.g. IL-4, IL-10 and TGF β , may inhibit IDO (Liebau et al., 2002; Oxenkrug, 2010). Thus, in a state of cell immune activation with overproduction of pro-inflammatory cytokines, the determining enzyme of TRY metabolism is IDO. Moreover, during the inflammatory responses, while IDO is activated, TDO appears to be suppressed (Takikawa et al., 1986, 1988; Brandacher et al., 2007). Oxidative and nitrosative stress, related to depression and other chronic inflammatory conditions (Maes et al., 2011a; Du and Pang, 2015) may also contribute to the IDO induction (Daley-Yates et al., 1988; Thomas and Stocker, 1999; Maes et al., 2007).

Consistent with these findings, TRY levels in depressed patients are inversely related to serum concentrations of pro-inflammatory markers, such as IL-6 and haptoglobin (a positive acute phase protein), and positively related to the levels of anti-inflammatory markers, such as transferrin (a negative acute phase inflammatory protein) (Maes et al., 1993; Seidel et al., 1995). Furthermore, reduced TRY levels have been frequently associated with increased levels of IFN- γ and neopterin, important markers of Th-1 immune response (Maes et al., 1994; Widner et al., 2002; Celik et al., 2010). The pro-inflammatory status in depression thus may stimulate IDO and consequently TRY catabolism (Maes et al., 2007, 2011b; Oxenkrug, 2010).

3.2. IDO activation and increased TRY metabolism in obesity

Recent studies have suggested that TRY metabolic imbalance may also be involved in the development of metabolic disorders, particularly obesity (Brandacher et al., 2007; Oxenkrug, 2013; Mangge et al., 2014a, 2014b). Classically, excessive nutrient intake and lack of exercise are key factors in the natural history of obesity. In obese individuals and related metabolic disorders the circulating levels of TRY are often reported as being reduced (Caballero et al., 1988; Wurtman et al., 2003; Oxenkrug, 2010; Sulo et al., 2013; Mangge et al., 2014b; Raheja et al., 2015) and as in depression, an imbalance of TRY metabolism has been proposed (Oxenkrug, 2010; Mangge et al., 2014b).

Obesity has been consistently considered as a chronic inflammatory disease characterized by increased levels of Th1 cytokines, such as IFN- γ and TNF α as well as other T lymphocytic and monocytic cell markers (Cancello and Clément, 2006; Rocha et al., 2008; Liu et al., 2014; Donma et al., 2015; Zahorska-Markiewicz et al., 2000). There is evidence supporting that Th1 cytokines, including IFN- γ , play a key role in the immune-inflammatory pathophysiology of obesity (Svec et al., 2007; Strissel et al., 2010; Lee and Lee, 2014). This is reinforced by preclinical findings showing that genetically or diet-induced obese mice produce more pro-inflammatory cytokines, including IFN- γ and TNF α , than control mice (Kawanishi et al., 2010; Yamada et al., 2016; Zhou et al., 2015). Furthermore, administration of TNF α or IL-6 to pregnant rats results in considerable expansion of adipose tissue in their offspring and increased vulnerability to obesity (Dahlgren et al., 2001). Higher serum levels of IFN- γ and IL-6 were observed in obese individuals when compared to healthy individuals. This increase in serum levels of pro-inflammatory cytokines was related to circulating levels of leptin, a hormone derived from adipose tissue related to differentiation of T naive cells towards a Th1 phenotype (Park et al., 2005; Pacifico et al., 2006; Rocha et al., 2008).

In this context, genetic factors, diet and physical inactivity among others are mechanism proposed to explain the systemic inflammatory status associated with obesity. Recently, diet is calling great attention since it can modulate the status of the resident gut flora and the translocation of toxigenic bacterial products through intestinal epithelium (Turnbaugh et al., 2008; Cani et al., 2009; Silventoinen et al., 2010; Lopresti et al., 2013; Lecomte et al., 2015). In fact, it was shown that high fat diets can affect the profile of microbial community favoring the growing of more toxigenic bacteria and facilitating the transport of bacterial products, especially the endotoxin LPS, to systemic circulation (Moreira et al., 2012). Furthermore, saturated fatty acids (SFA), an important component of diet-induced obesity, directly induce pro-inflammatory changes in adipocytes and adipose tissue macrophages. These fatty acids can activate nuclear factor- κ B (NF- κ B), a transcription factor necessary for the expression of several inflammatory cytokines like IFN- γ and TNF α as well as for the stimulation of the secretion of macrophage chemotactic factors, such as monocyte chemoattractant protein 1 (MCP-1/CCL2). Interestingly, the action of SFA seems to be mediated, similarly to LPS, by toll-like receptor 4 (TLR4). This is confirmed by findings showing that the inhibition of TLR4 prevents the development of pro-inflammatory changes in adipocytes (Yeop Han et al., 2010; Caesar et al., 2015).

It has been proposed that the imbalance of TRY metabolism observed in obese patients is consequent to IDO activation by pro-inflammatory cytokines. Thus, this imbalance of TRY metabolism could be a major risk factor associated to obesity. In this regard, animals subjected to genetic models of obesity have significantly reduced serum TRY levels as compared to controls as well as increased levels of serum pro-inflammatory cytokines (Finkelstein et al., 1982; Bigorgne et al., 2008; Lawrence et al., 2012; Favero et al., 2015). Additionally, in elderly and young adult patients, IDO activity (as indicated by the KYN/TRY ratio) was strongly associated with metabolic risk factors, such as elevated low-density lipoprotein, higher abdominal circumference and elevated CRP (Pertovaara et al., 2007; Niinisalo et al., 2008; Sulo et al.,

2013). Also, morbidly obese patients seem to present high serum levels of neopterin and KYN and reduced serum levels of TRY. Interestingly, these alterations remain even after bariatric surgery (Brandacher et al., 2006). Furthermore, a recent study analyzing adipose tissue and liver samples found increased IDO expression, pro-inflammatory cytokines (IL-18, TNF α) and T cell activation markers (CD14, CD68, and CD3 ϵ) in samples of obese patients (Wolowczuk et al., 2012). Therefore, similarly to depression, systemic immune activation in obesity may stimulate IDO thereby inducing an imbalance of TRY catabolism.

3.3. TRYCAT pathway in depression and obesity: 5-HT depletion and the production of detrimental TRYCATs

Kynurenine is a substrate for the production of KYNA and nicotinamide-adenine dinucleotide (NAD). KYNA synthesis is regulated by the enzymes kynurenine aminotransferase (KAT) I, II and III. The enzymes kynurenin-3-monooxygenase (KMO), kynureninase and kynurenine hydroxylase generate NAD as final product. Together, these routes can generate > 30 intermediate metabolites, collectively called TRYCATs, with multiple biological actions, some of which deleterious (Maes et al., 2007; Oxenkrug, 2007).

In the CNS, the TRYCATs can mediate important effects. For example, QUIN and picolinic acid, both derived from NAD pathway, are endogenous agonists of glutamate NMDA receptors. In addition, QUIN can inhibit glutamate uptake by astrocytes potentiating the toxic effects of the overactivation of NMDA receptors (Tavares et al., 2002, 2005). QUIN can cause the destruction of postsynaptic neural elements and the death of hippocampal and granular progenitor cells (Khaspekov et al., 1989; Santamaría et al., 2001; Steiner et al., 2011; Lugo-Huitrón et al., 2013; Meier et al., 2016). Other metabolites of NAD pathway, such as 3-HK and 3-hydroxyanthranilic acid, generate free radicals and induce pro-apoptotic effects in neuronal cells being associated with the development of neurodegenerative diseases, e.g. Huntington's and Alzheimer's disease (Goldstein et al., 2000; Yan et al., 2005; Smith et al., 2009; Gulaj et al., 2010; Tan et al., 2012; Reyes-Ocampo et al., 2015). On the other hand, KYNA is an endogenous NMDA receptor antagonist presenting antioxidant properties. These antioxidant properties of KYNA can counteract the excitotoxicity induced by the toxic metabolites of NAD pathway (Henderson et al., 1990; Małaczewska et al., 2014; Savitz et al., 2015a). However, KYNA was also related to the antagonism of $\alpha 7$ nicotinic receptors. This nicotinic receptor has a key role in central cholinergic anti-inflammatory response (Hilmas et al., 2001) (an overview of TRYCATs pathway can be seen in Fig.1).

Fig. 1. Overview of the tryptophan catabolite (TRYCAT) pathway including methoxyndole pathway. Enzymes are written in *italic* and asterisks indicate the step-limiting enzymes. IDO: indoleamine 2,3-dioxygenase; TDO: tryptophan 2,3-dioxygenase; KAT: kynurenine aminotransferase; KMO: kynurenine 3-monooxygenase; 3-OH-KYN: 3-hydroxykynurenine; 3-HAO: 3-hydroxyanthranilic acid oxygenase; QPRT: quinolinic phosphoribosyltransferase; NaMN: nicotinamide mononucleotide; NMNAT: nicotinamide mononucleotide adenyltransferase; NAD: nicotinamide adenine dinucleotide; TH: tryptophan hydroxylase; 5-HTP: 5-hydroxy-L-tryptophan; AADC: aromatic L-amino acid decarboxylase; MAO: monoamine oxidase; AA-NAT: aralkylamine *N*-acetyltransferase; NAS: *N*-acetylserotonin; HIOMT: hydroxyindole *O*-methyltransferase.

3.3.1. Increased detrimental TRYCATs in depression

Previous research has indicated that some TRYCATs can affect animal behavior towards anxiogenic- and depressive-like phenotypes. The first evidence of this effect came from studies demonstrating that peripheral or intracerebroventricular administration of KYN and QUIN could induce anxiogenic-like effect in rodents in the open field and elevated plus maze tests (Vécsei and Beal, 1990; Lapin et al., 1996). More recently, O'Connor et al. (2009b) reported that the peripheral administration of L-KYN triggers depressive-like behavior in rodents in a dose-dependent manner. These investigators also observed that the behavioral alterations caused by peripheral administration of LPS depend on the central activation of IDO being reversed by 1-methyl-tryptophan, a competitive IDO inhibitor, or by minocycline, a tetracycline with notable anti-inflammatory effects (O'Connor et al., 2009b).

Immune activation triggered by LPS is capable of inducing enzyme activities of IDO and kynurenine hydroxylase (one of the main enzymes involved in NAD pathway), but not kynurenine aminotransferases (the main enzymes involved in the KYNA pathway). These findings suggest that immune challenge with LPS selectively stimulates TRY catabolism towards NAD pathway resulting in the production of neurotoxic TRYCATs (Connor et al., 2008). A possible explanation for this phenomenon is that, in situations of brain immune challenge, microglia orchestrate neuro-inflammatory changes in the brain. Microglia mainly express the enzymes of NAD pathway, as KMO and kynurenine hydroxylase. The opposite occurs in astrocytes, in which KAT predominates. Consequently, in animal models of depression induced by LPS, microglia is responsible for the production of neurotoxic metabolites derived from NAD pathway, such as QUIN and 3-HK (Guillemin et al., 2001; O'Connor et al., 2009b; Steiner et al., 2011; Salazar et al., 2012).

Clinical evidence supports the hypothesis that the increased production of neurotoxic TRYCATs may occur in depression (Mackay et al., 2009; Gabbay et al., 2010; Meier et al., 2016; Savitz et al., 2015c). In this context, Gabbay et al. (2010) found high rates of KYN/TRY (indicator of IDO activity) and of 3-HK/KYN in adolescent patients with depression, which reflects the occurrence of TRY metabolism through NAD pathway in depression. Additionally, these increased ratios were positively associated with the severity of depressive symptoms (Gabbay et al., 2010). High serum levels of hydroxyanthranilic acid and QUIN were also demonstrated in adult patients with depression and being associated with the worsening of mood symptoms (Mackay et al., 2009; Savitz et al., 2015c). Furthermore, some evidence indicates that not only TRY levels are reduced, but also KYNA levels are compromised in patients with depression (Myint et al., 2007; Savitz et al., 2015c).

Some of the most interesting findings about the participation of

TRYCATs in depression came from studies with patients using immunotherapy. Immunotherapy mimics the systemic immune activation observed in chronic inflammatory disorders, such as depression. In these patients, the onset and severity of depressive symptoms correlates strongly with IDO activity and TRYCATs production (Bonaccorso et al., 2001; Bonaccorso et al., 2002; Wichers et al., 2005; Vignau et al., 2009; Raison et al., 2010; Maes et al., 2011b). Bonaccorso et al. (2002) and Wichers et al. (2005) demonstrated that the onset of depressive symptoms during IFN- α -based immunotherapy was positively associated with the KYN/TRY and KYN/KYNA ratios. Since KYN is the substrate for QUIN synthesis these results allow us to better visualize the association between the increase in detrimental TRYCATs and the development of depressive symptoms over time (Bonaccorso et al., 2002; Wichers et al., 2005). Also, Raison et al. (2010) reported a significant association between serum levels of QUIN and the emergence of depressive symptoms in patients undergoing IFN- α -based immunotherapy (Raison et al., 2010). Therefore, systemic immune activation in depression may selectively induce TRY metabolism towards the production of potentially detrimental TRYCATs, which are associated with the onset of depressive symptoms.

3.3.2. Increased detrimental TRYCATs in obesity

Besides central effects, TRYCATs also exert effects on peripheral organs. Previous studies have shown an increase in the production of detrimental TRYCATs in the course of obesity and related metabolic disorders (Oxenkrug, 2010, 2013; Mangge et al., 2014a, 2014b). Enzymes involved in TRYCAT synthesis are constitutively expressed in key metabolic organs, such as liver, pancreas and adipose tissue and are activated by pro-inflammatory cytokines (Däubener and MacKenzie, 1999; Fujigaki, 2006; Wolowczuk et al., 2012; Liu JJ et al., 2015). It was also reported that KYN, QUIN and picolinic acid can stimulate nitric oxide synthase (NOS) activity resulting in an increased production of nitric oxide and nitrous free radicals in macrophages and endothelial cells (Melillo et al., 1994; Chiarugi et al., 2000). In pancreatic cells, TRYCATs such as 3-hydroxyanthranilic, picolinic and xanthurenic acid can promote a cascade of arachidonic acid reactions, increasing the production of pro-inflammatory factors, such as prostaglandins and leukotrienes (Melillo et al., 1993; Alberati-Giani et al., 1997; Bosco et al., 2000, 2003; Cesario et al., 2011). On the other hand, KYNA has anti-inflammatory and immunomodulatory actions in peripheral immune cells (Małaczewska et al., 2014).

Some diet components may contribute to the synthesis of detrimental TRYCATs in key metabolic organs, including the pancreas. For example, Liu et al. (2015a,b) reported that high concentrations of glucose and SFA stimulate the expression of IDO and KMO leading to an increased KYN/KYNA ratio in cultured β -pancreatic cells. Oxidative stress and glucocorticoids also induce the expression of these enzymes and TRYCATs production in pancreatic cells (Liu JJ et al., 2015). Importantly, TRYCATs have important metabolic effects. For example, acute exposure to TRYCATs, including 3-hydroxykynurenine and 3-hydroxyanthranilic acid, inhibits the secretion of insulin by β -pancreatic cells (Rogers and Evangelista, 1985; Liu et al., 2015a). Additionally, xanthurenic acid may compromise the biological activity of insulin, forming an antigenic complex with this hormone. Together, these mechanisms may be potentially involved in the onset of insulin resistance in obesity and metabolic syndrome (Kotake et al., 1975; Meyramov et al., 1998; Oxenkrug, 2013).

There is some evidence that increased TRYCATs production may also be causally associated with the onset of obesity and related metabolic disorders (Mangge et al., 2014b; Favennec et al., 2015). In this context, Favennec et al. (2015) demonstrated increased levels of KYN, KYNA and QUIN in serum of obese patients as compared to healthy controls. Positive correlations between the serum levels of KYN and QUIN and body mass index (BMI) as well as insulin resistance were found. Analyzing the omental adipose tissue of obese patients, a considerable expression of several enzymes involved in the TRYCAT

pathway was found, including IDO, kynureninase, KMO and KTA III (Favennec et al., 2015). Other recent studies demonstrate high serum levels of TRYCATs, including KYNA and xanthurenic acid, in patients with type 2 diabetes mellitus and coronary atherosclerosis. The increased levels of detrimental TRYCATs in metabolic disorders were also associated with a worse outcome of these metabolic diseases (Eussen et al., 2015; Oxenkrug, 2015).

The link between the activation of TRYCATs pathway and the development of weight gain/obesity has been reinforced by recent studies using genetic-based approaches. For example, Nagano et al., 2013 reported that *Ido1*^{-/-} mice present less weight gain compared with wild-type mice when submitted to Western diet (for 26 weeks). This was confirmed by the study of Moyer et al. (2016), that additionally demonstrated the relevance of aryl hydrocarbon receptor (AHR) pathway to the IDO/TRYCATs effects in the context of diet-induced obesity. Of note, it was demonstrated that AHR antagonists, such as α -naphthoflavone or CH-223191, prevent the development of obesity and adiposity and ameliorates liver steatosis in mice fed with Western diet (Moyer et al., 2016). Interestingly, Moyer and coworkers demonstrated that the genetic or pharmacological blockade of IDO1 reduces the expression of AHR in mouse hepatocytes. Other relevant pathways, such as TGF β 1 and TLR2/4 signaling also exert their effects on AHR expression through IDO induction and KYN production (Moyer et al., 2016). Therefore, AHR activation through TRYCATs synthesis seems to be a unifying mechanism for the effects of inflammatory-related pathways in diet-induced weight gain.

Obesity is not just associated with chronic inflammation in peripheral tissues, but also with central inflammation. Upregulated levels of IL-6, TNF α and NF- κ B are detected in the brain of genetically obese rodents or rodents subjected to diet-induced obesity (Zhang et al., 2008; Boitard et al., 2014; Maric et al., 2014; Dorfman and Thaler, 2015). Reactive gliosis with infiltration of peripheral immune cells and proliferation of resident glial cells is found in the brain of obese animals (Buckman et al., 2014; Dorfman and Thaler, 2015). Clinical *postmortem* studies corroborate these findings, showing considerable glial activation and neuronal injury in brain tissue of obese individuals (Thaler et al., 2012).

There is compelling evidence that central neuroinflammation is an important factor in the onset of neuropsychiatric symptoms related to obesity (Soczynska et al., 2011; Miller and Spencer, 2014; Castanon et al., 2015). Among the several neuroinflammatory processes involved in obesity, IDO activation and subsequent TRYCAT production in the CNS may be relevant to the onset of mood and anxiety (Lin et al., 2007; Swardfager et al., 2009; Dinel et al., 2011, 2014). Preclinical studies demonstrate that in genetically obese mice the induction of depressive-like behavior following systemic LPS administration is intrinsically related to IDO activation following increases in pro-inflammatory cytokines (IL-1 β and TNF α) in the hippocampus (Dinel et al., 2014). A significant reduction in hippocampal expression of brain derived neurotrophic factor (BDNF), which has been consistently related to depression pathophysiology (Moylan et al., 2013; Dinel et al., 2014). Similarly, other recent evidence demonstrated that animals subjected to diet-induced obesity present significant behavioral changes, depressive-like and anxiogenic-like behavior, concomitantly to the increase in the expression of several pro-inflammatory cytokines and IDO activity in the hypothalamus and hippocampus (André et al., 2014).

Clinical evidence supports the association between neuroinflammation in obesity and the occurrence of neuropsychiatric symptoms. In order to confirm this association previous studies showed that inflammatory markers, such as serum levels of CRP and IL-6, have been strongly associated with the onset and severity of depressive symptoms in obese patients (Ladwig et al., 2003; Dixon et al., 2008; Abdullah et al., 2009; Chirinos et al., 2013; Castanon et al., 2014). Furthermore, interventions that attenuate this inflammation, such as low-caloric diet and physical exercise, improve the emotional status of obese patients (Pibernik-Okanovic et al., 2009; Lopresti et al., 2013; Oertel-Knöchel

Fig. 2. Mechanisms underlying chronic systemic inflammation involved in obesity and depression leading to central and peripheral IDO activation and production of potentially detrimental TRYCATs. Etiological risk factors, e.g., fat/sugar diet, physical inactivity, social/psychological stress or chronic infections can originate a state of systemic inflammation involved in the development of obesity-depression comorbid. The peripheral release of proinflammatory cytokines can activate IDO pathway in key metabolic organs, such as adipose tissue, as well as access the brain via several pathways (e.g., neural, humoral, and cellular routes). In the CNS cytokines can induce neuroinflammatory processes, primarily by activating microglia and after by promoting the induction of IDO activity and synthesis of neuroactive/neurotoxic TRYCATs. Deregulations of the gut-brain axis, by changes in gut microbiota composition and permeability, can also participate in induction of systemic inflammatory state and activation of TRY metabolism through IDO and TRYCATs pathway. IDO: indoleamine 2,3-dioxygenase; KAT: kynurenine aminotransferase; KMO: kynurenine 3-monooxygenase; KYN: kynurenine; KYNA: kynurenic acid; LPS: lipopolysaccharide; PAMPs: pathogen-associated molecular pattern; QUIN, quinolinic acid; TRY: tryptophan.

et al., 2014; Strassnig et al., 2015; Vučić Lovrenčić et al., 2015). Nevertheless, as far as we know there are no studies showing IDO activation and TRYCATs synthesis in the brain of obese patients as well as their relationship with the emergence of psychiatric symptoms (Fig. 2). This could be a potential mechanism in this comorbid being thus an important issue to be addressed in further studied.

3.4. TRYCAT pathway and cognitive deficits in depression and obesity

Cognitive functions in humans comprise different domains such as perception, attention, memory and executive function (Cohen et al., 1996; Guan et al., 2016). Several studies have shown that depression is associated with impairments in cognitive functions, especially frontally-mediated cognitive domains, including memory, executive functioning and planning. Furthermore, some deficits present early in the course of the disorder and may worsen with staging (Papakostas, 2006; Bora et al., 2013). In this context, a recent meta-analysis, focusing in the cognitive deficits present in early depression, analyzed the

data from 13 different studies involving > 640 patients (Lee RSC et al., 2012). These researchers found that patients with MDD had in the first mood episode significant impairment in psychomotor speed (effect size 0.48), attention (effect size 0.36), and visual learning and memory (effect size 0.53). Also, within the domain of executive functions, attentional switching (effect size 0.22), verbal fluency performance (effect size 0.59) and cognitive flexibility (effect size 0.53) were worse in these patients (Lee RSC et al., 2012). Declarative memory and psychomotor speed deficits frequently become more severe with long-term illness duration, and sometimes associate with relapses or recurrences following antidepressant treatment (MacQueen et al., 2002; Trivedi and Greer, 2014; Kim et al., 2016). In fact, a study conducted with older individuals showed that patients with poor executive function measured at the beginning of antidepressant treatment were more likely to have a relapse over a 16-week continuation phase and more likely to experience a recurrence over a 2-year maintenance phase as compared to those with normal executive functions (Alexopoulos et al., 2000).

Cognitive deficits have an important impact on functionality and

occupational productivity in patients with depression (Evans et al., 2013; Trivedi and Greer, 2014). Evans et al. (2013) in a systemic review showed considerable evidence that cognitive problems in depressive patients was associated with significant work impairment and potential loss of employment (Baune et al., 2010; Godard et al., 2012; Evans et al., 2013). Additionally, McIntyre et al. (2013) reported that cognitive impairment, particularly in executive function, working memory, attention and psychomotor processing are the primary factor for diminished workforce performance in patients with depression (McIntyre et al., 2013), and persists even in euthymic phases (Bora et al., 2013). Attention deficit also been associated with impaired work productivity in these patients (Trivedi et al., 2013).

Obesity is also associated with poor neurocognitive outcomes in several cognitive domains (Dore et al., 2008; Spitznagel et al., 2015). In adult individuals, deficits in fronto-temporal-mediated cognitive functions, such as executive functions and processing speed, have been consistently associated with obesity (Gunstad et al., 2007; Prickett et al., 2015). Learning and memory deficits are present in young to middle-aged obese patients, especially in severely obese individuals (i.e. bariatric surgery candidates) (Gunstad et al., 2006). Additionally, in children (between the ages of 6 and 10 years), obesity and overweight are associated with greater impairment in inhibitory control relative to age-matched and gender-matched controls (Blanco-Gómez et al., 2015).

Longitudinal studies indicate that obesity may accelerate the progression of age associated cognitive decline (Spitznagel et al., 2015). In this context, Gunstad et al. (2010) demonstrated in a sample of 1703 older adult patients that higher obesity indices (i.e. BMI, waist-to-hip ratio) predicted an accelerated decline in global cognitive function, executive function and memory across several assessment time points (Gunstad et al., 2010). However, these authors notice that obese patients have a better performance on tests of attention and visuospatial ability (Gunstad et al., 2010). Another large study with middle-older adult patients (2223 participants aged 32 to 62 years) reported that higher baseline BMI predict a faster memory decline over time even after adjusting for demographic and medical variables (Cournot et al., 2006). There is considerable evidence that midlife obesity is a strong risk factor for subsequent dementia, such as Alzheimer's disease and vascular dementia (Anstey et al., 2011; Tolppanen et al., 2014). An extensive meta-analysis of 15 prospective studies revealed that an overweight BMI in midlife was associated with a 1.35 times increased risk for Alzheimer's disease, a 1.33 higher risk for vascular dementia and 1.26 greater risk for all cause dementia (Anstey et al., 2011). Importantly, the increased risk for dementia associated with obesity appears to be independent of other medical conditions, such as hypertension, stroke, heart disease and diabetes (Whitmer et al., 2005).

Despite the fact that the pathways by which depression and obesity impact cognition are not completely understood, there are data supporting the participation of neuroimmune mechanisms and chronic inflammation in the initiation and progression of cognitive deficits involved in both of these diseases (Soczynska et al., 2011). Indeed, although at physiological levels some cytokines, e.g. IL-6, play a key role in the synaptic plasticity and neurogenesis in brain circuits, at higher levels, it can compromise neuronal survival and synaptic transmission, causing learning and memory impairments (Avital et al., 2003; Yirmiya and Goshen, 2011). Recent studies show that IDO activation and subsequent production of neurotoxic TRYCATs may mediate the neurotoxic effects of cytokines causing deleterious effects on neural circuits (Stone and Darlington, 2013; Young et al., 2016).

In this context, an interesting study conducted by Zunszain et al. (2011) shows that the exposition of human hippocampal progenitor cells to the pro-inflammatory cytokine IL-1 β promoted a marked increase (12–30-fold) in the expression of several enzymes of KYN pathway, especially, those implicated in 3HK and QUIN production, IDO, KMO and kynureninase (Zunszain et al., 2011). These effects were followed by an important impairment in hippocampal neurogenesis, as

shown by reduction in the number of doublecortin-positive neuroblasts and mature microtubule-associated protein-2-positive neurons. The treatment with a KMO inhibitor reversed these detrimental effects of IL-1 β on neurogenesis (Zunszain et al., 2011). Accordingly, in animal studies, mice challenged with systemic LPS administration showed impairments in cognitive domains, such as learning, recognition and working memory, as well as synaptic function (Deng et al., 2012; Zhu et al., 2014). An important increase in IDO expression/activity and TRYCATs production was described in frontal-hippocampal regions of LPS-treated mice (André et al., 2008; O'Connor et al., 2009b). Additionally, a recent study showed that LPS-induced cognitive deficits in mice can be mimicked by the central injection of L-KYN being blocked by genetic deletion of IDO or KMO enzymes (Heisler and O'Connor, 2015).

Consistent with these findings, in clinical studies, immunogenic agents, like low-dose LPS or typhoid vaccine, has been shown in healthy patients to impair cognitive functions, such as short-term recall and memory (Reichenberg et al., 2001; Harrison et al., 2014). These cognitive abnormalities are accompanied by induction of pro-inflammatory cytokines and glucose metabolism alterations in brain regions associated with cognitive processes, including the medial temporal lobe (MTL) and frontal regions (Reichenberg et al., 2001; Harrison et al., 2014). In depressive patients, some morphometric MRI studies have demonstrated the association between volume reductions in brain areas associated with memory and executive function, such as hippocampus (Savitz et al., 2015b) and prefrontal cortex (Meier et al., 2016), and increased circulating levels of QUIN and KYN levels. In addition, a recent study integrated the data from neuropsychological alterations in depressive patients with brain image analysis and TRYCATs circulating levels (Young et al., 2016). These authors analyzed the autobiographical memory (AM) recall and found that the deficit in this cognitive domain was related to increased activity in left hippocampus in fMRI scanning and increase of plasma KYN/KYNA ratio. Additionally, the percent negative memories recalled were positively correlated with ratio of KYNA/QUIN (Young et al., 2016). Detrimental TRYCATs (e.g. KYN and QUIN) cause NMDA excitotoxicity, oxidative damage and the initiation of inflammatory responses (Santamaría et al., 2001; Tavares et al., 2005; Steiner et al., 2011), while KYNA has neuroprotective properties (Hilmas et al., 2001; Savitz et al., 2015a), indicating that selective activation of the KYN pathway towards the production of potentially neurotoxic metabolites, such as QUIN, may compromise cognitive functions in depression.

Neuroinflammatory alterations have been linked to cognitive impairment and increased risk for dementia in obese people (Castanon et al., 2014; Miller and Spencer, 2014). In preclinical studies there is evidence that obesity-associated neuroinflammation, especially in medial-temporal brain regions, such as hippocampal-parahippocampal circuits, is implicated in cognitive alterations seen in this disease. Indeed, it was demonstrated that animals submitted to high fat diet (in different duration protocols) presented several cognitive disturbances, for example impaired spatial learning and long-term memory (Boitard et al., 2012, 2014b; Valladolid-Acebes et al., 2013) and contextual fear conditioning memory (Hwang et al., 2010). This impairment has been associated with increased pro-inflammatory markers in the hippocampus, e.g. pro-inflammatory cytokines (IL-1 β , TNF α) and Iba1 expression (a marker of microglial activation) (White et al., 2009; Jeon et al., 2012). Additionally, these cognitive deficits and neuroinflammatory abnormalities have been reversed or attenuated by anti-inflammatory and antioxidant agents (Jeon et al., 2012). A recent study showed that, in severe obese people (BMI > 35 kg/m²), the performance in neuropsychological tests for cognitive flexibility and shifting abilities was negatively related with the serum levels of CRP, as a marker of systemic low-grade inflammation (Lasselín et al., 2016). In addition, studies demonstrating that in overweight subjects increased markers of systemic inflammation, such as IL-6 and CRP, were inversely associated with serum polyunsaturated fatty acids versus saturated fatty

acids (PUFA:SFA) ratio (Klein-platat et al., 2005). Additionally, low levels of circulating PUFAs, mainly eicosapentaenoic and docosahexaenoic acid, were associated with poor cognitive performance in overweight and obese patients (Haapala et al., 2016).

In obese individuals, there are no studies regarding IDO activation and the production of detrimental TRYCATs in relation to obesity-associated cognitive decline. Nevertheless, mice submitted to a Western diet (consisting of palatable energy-dense food, and with 49% from fat) developed impairments in spatial recognition memory after 9 and 18 weeks of altered diet (André et al., 2014). Western diet-fed mice presented exacerbated hippocampal and hypothalamic expression of pro-inflammatory cytokines (IL-1 β and IL-6) and IDO activation (increased KYN/TRY ratio) when challenged with LPS (André et al., 2014). However, another recent study investigating the effects of short-term (1–3 weeks) high fat diet (HFD) in adolescent mice, showed that IDO knockout mice were not protected from HFD-induced spatial memory impairment, leading to the conclusion that IDO activation is not a prerequisite to develop cognitive deficits after a short-term HFD (Kaczmarczyk et al., 2013). These discrepancies can be attributed to differences in duration of feeding protocols (e.g. short-duration used in the latter study), as well as the differences in nutritional composition of the diet used. Furthermore, other cognitive domains, such as executive function and affective memory, which were not analyzed, could be more profoundly affected by IDO activation in the context of neuroinflammatory abnormalities involved in obesity.

In sum, depression and obesity are both conditions in which cognitive impairment is frequently observed impacting quality of life outcomes. Compelling evidence has highlighted the involvement of neuroinflammatory mechanisms in the genesis of cognitive alterations seen in these diseases. IDO activation and production of detrimental TRYCATs may play a role in these neurocognitive deficits.

3.5. IDO activation and the TRY methoxyindole pathway

The methoxyindole pathway, as previously mentioned in this review, has as main products serotonin and its derivatives, which are already classically involved in the neurobiology of depression and in the mechanism of antidepressant drugs. Apart from this, it has been proposed that derivatives of this pathway also perform important regulatory effects on the regulation of hunger and satiety (Fernstrom and Fernstrom, 1995; Halford et al., 2005; Choi et al., 2009; Mange et al., 2014b). For example, 5-HT physiologically regulates the intake of carbohydrates and fats. This neurotransmitter is also able to alleviate the stress stimulating effects on calorie intake by inhibiting neuropeptide Y (NPY), which has strong orexigenic effect in the hypothalamus (Jourdan et al., n.d.; Buwalda et al., 2001; Jia et al., 2010). Furthermore, melatonin, a 5-HT derivative, beyond regulating sleep-wake cycle, has an important role in the modulation of food intake stimuli. The endogenous production of melatonin and sleep duration are inversely related to the caloric intake in humans and animals (Sutcliffe and de Lecea, 2000; Zeitzer et al., 2007; Cipolla-Neto et al., 2014). MT2 melatonin receptors are constitutively expressed in human adipose tissue and regulate the metabolism of these cells, indicating that adipose tissue is also a direct target of the chronobiological effects of this hormone (Brydon et al., 2001; Song and Bartness, 2001).

Therefore, other important consequence of an imbalance of TRY metabolism, in conditions of chronic immune activation, is the depletion of TRY in the methoxyindole pathway and the subsequent reduction of serotonergic-melatonergic tone. This depletion not only leads to neurochemical changes involved in depression, but also to central and peripheral alterations, such as an increase of central orexigenic stimuli and disruption of chronobiological cycle of adipose cells. The latter pathways may directly or indirectly contribute to the onset and maintenance of obesity and its neuropsychiatric consequences.

3.6. TRYCAT pathway as a drug target for depression and obesity

Therapies targeting immune-inflammatory pathways can potentially have antidepressant and metabolically favorable effects (Channul et al., 2009; Soczynska et al., 2011). Adjunctive treatments with the cyclooxygenase-2 (COX-2) inhibitor, celecoxib, may exert antidepressant effects in MDD (Nery et al., 2008; Akhondzadeh et al., 2009) and improves metabolic and cardiovascular characteristics in obese patients (Hsieh et al., 2009; Cunha et al., 2010). The administration of insulin sensitizers (e.g. thiazolidinediones), which also have anti-inflammatory properties, may improve neurocognitive functions (McIntyre et al., 2007) and exert antidepressant effects (García-Bueno et al., 2007; Zeinoddini et al., 2015). Minocycline, a second-generation tetracycline and potent microglia inhibitor, may have antidepressant effects in clinical (Husain et al., 2015) and experimental setting (Majidi-zolbanin et al., 2015; Zheng et al., 2015). Some evidence also indicates that minocycline may also be beneficial for patients with coexisting metabolic (e.g. type 2 diabetes mellitus) and other inflammatory conditions (Soory, 2008; Matsumoto et al., 2009).

Therefore, the TRYCAT pathway and IDO activation may be an important drug target for the development of new antidepressants. Depressed patients treated with the antidepressant sertraline show a reduction in the KYN/melatonin ratio and 3-hydroxykynurenine/melatonin ratio, compared to pretreatment (Zhu et al., 2013). On the other hand, the TRYCAT pathway was unchanged in depressed patients resistant to sertraline (Zhu et al., 2013). Also, patients treated with fluoxetine for 18 weeks showed a positive correlation between KYN serum levels and psychiatric rating scores for depressive symptoms (Mackay et al., 2009). Interestingly, single nucleotide polymorphism (SNP) in IDO1 and IDO2 predict the response to citalopram (Cutler et al., 2012).

Accordingly, in a preclinical model of depression the antidepressant paroxetine reversed the increase in KYN concentrations and depletion of KYNA in brain and serum samples (Franklin et al., 2012). Also, the antidepressant citalopram exerted antidepressant-like effects and increased turnover of 5-HT via IDO inhibition in the hippocampus, amygdala and hypothalamus of stressed rats (Ara and Bano, 2012). In microglial cell cultures, fluoxetine alone or in combination with acetylsalicylic acid inhibited microglial activation and attenuated LPS-induced production of IL-1 β , expression of IDO, and the depletion of 5-HT (Yang et al., 2014).

Considerable evidence shows that fluoxetine (Rosmond and Björntorp, 2000), tricyclic agents, including butriptyline, protriptyline and nortriptyline (Dulloo and Miller, 1987) and 5-HT-NE receptors agonists (D-Fenfluramine, sibutramine) have anti-obesity and weight loss-inducing properties (Blundell and Lawton, 1995; Halford et al., 2005; Sargent and Henderson, 2011; Burke et al., 2014). These properties have been related to potentiation of 5-HT neurotransmission and inhibition of hunger-induced stimuli in hypothalamus (Jourdan et al., n.d.; Buwalda et al., 2001; Jia et al., 2010) and sympathetic activation-induced thermogenesis in adipose tissue (Heal et al., 1998). There is also evidence that some monoaminergic-based antidepressants increase the risk of metabolic syndrome and weight gain in depressive patients (Corruble et al., 2015; Himmerich et al., 2015). On the other hand, FDA approved the combination of naltrexone and the antidepressant bupropion (a norepinephrine-dopamine reuptake inhibitor), to treat obesity (Narayanawami and Dwoskin, 2016). Deserves mention the fact that bupropion is an indirect inhibitor of IDO since this drug lowers the production of IFN- γ and TNF α (Brustolim et al., 2006).

Furthermore, direct modulators of the TRYCAT pathway may have beneficial effects in animal models of depression and neuroinflammation and therefore could be new drugs to treat depression. In this context, in mice infected with BCG, a model of peripheral and brain inflammation, IDO inhibition by the pharmacological competitive antagonist 1-methyl-tryptophan (1-MT) blocked the emergence of depressive-like behavior. Similarly, the IDO-deficient mice did not

demonstrate this depressive phenotype (O'Connor et al., 2009c). It was also shown that IDO inhibition by 1-MT reverses the anhedonic- and anxiety-like behavior induced by systemic (O'Connor et al., 2009b) and intracerebroventricular (Lawson et al., 2013) injection of LPS. In fractalkine receptor deficient mice (CX3CR1(−/−)), which show an exacerbated inflammatory response and microglial activation after LPS immune challenge, IDO inhibition by 1-MT prevented the emergence of depressive-like behavior and reduced the microglial activation as well as the increases in 3-HK/TRP and 5-HIAA/5-HT ratios in prefrontal cortex and hippocampus (Corona et al., 2013). Allopurinol, a TDO inhibitor, also attenuates depressive-like behavior and reduces circulating KYN concentrations in rats submitted to repeated restraint stress (Gibney et al., 2014). Additionally, treatment with the KMO competitive inhibitor RO61–8048 reverses depressive-like behaviors as well as abnormalities in glutamatergic system, such as increased extracellular glutamate concentrations and altered levels of the glutamate receptors, in rats exposed to unpredictable chronic mild stress (UCMS) model of depression (Chen et al., 2013). 1-MT and minocycline, which has anti-inflammatory and indirect IDO inhibiting effects, exert important antidepressant-like effects in streptozotocin-induced diabetic rats. These drugs and the antidepressant fluoxetine attenuate the expression of IDO in the hippocampus of diabetic animals (da Silva Dias et al., 2015). Therefore, inhibition of IDO, may be a potential drug target for depression and neuropsychiatric symptoms in obesity.

Regarding obesity, some preliminary evidence pointed out to the protective effects of genetic deletion of IDO against the diet-induced weight gain and steatohepatitis in rodents (Nagano et al., 2013; Moyer et al., 2016). As far as we know, only one study showed weight depression action of 1-MDT in rats (Sankoff and Sourkes, 1962), thus, at the best of your knowledge, inhibitors of IDO were not tested in models of obesity. Similarly, in clinical setting, the application of selective inhibitors of IDO and related enzymes to treat obesity and metabolic disorders was not investigated, however recent evidence demonstrated that multimodal therapies, such as Mediterranean diet, based on the high intake of extra-virgin olive oil, fruits and cereals (Yu et al., 2017) and physical exercise (Mudry et al., 2016) could affect TRY metabolism, towards an increase in plasma TRY levels and reduction of detrimental TRYCATs production, especially KYN. Additionally, it was reported that some natural products, such as Berberine, an isoquinoline alkaloid isolated from *Berberis aristata*, a herb widely used in Indian and Chinese systems of medicine, could inhibit IDO significantly stronger than 1-MT (Yu et al., 2010). Interestingly, it was demonstrated that Berberine could improve insulin resistance and dyslipidemia in diabetic patients (Di Pierro Francesco et al., 2012), opening perspectives to its use in the context of obesity and metabolic syndrome.

4. Conclusions

This review shows that obesity and depression exhibit a clear bidirectional relationship. Systemic immune activation associated with the overproduction of inflammatory cytokines, especially a Th1 shift, play a role in the pathophysiology of both diseases. We suggest that IDO activation and subsequent activated TRY catabolism may be a potential mechanism for the development of mood symptoms in obese patients. Some TRYCATs impact key metabolic organs, including adipose tissue, pancreas and liver, and aggravate inflammatory responses compromising the functioning of these tissues. Consequently, it is probable that noxious TRYCATs may contribute to the development of metabolic disorders in depressive patients and increase risk for obesity. Given the alarming and progressive rise of obesity and depression in Western countries and the grave impact increasing risk of serious chronic diseases, the TRYCAT pathway may be a new drug target to counterbalance the consequences of inflammation related to comorbid obesity and depression.

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