Role of Adiposity-Driven Inflammation in Depressive Morbidity

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Depression and metabolic disorders, including overweight and obesity, appear tightly interrelated. The prevalence of these conditions is concurrently growing worldwide, and both depression and overweight/obesity represent substantial risk factors for multiple medical complications. Moreover, there is now multiple evidence for a bidirectional relationship between depression and increased adiposity, with overweight/obesity being associated with an increased prevalence of depression, and in turn, depression augmenting the risk of weight gain and obesity. Although the reasons for this intricate link between depression and increased adiposity remain unclear, converging clinical and preclinical evidence points to a critical role for inflammatory processes and related alterations of brain functions. In support of this notion, increased adiposity leads to a chronic low-grade activation of inflammatory processes, which have been shown elsewhere to have a potent role in the pathophysiology of depression. It is therefore highly possible that adiposity-driven inflammation contributes to the development of depressive disorders and their growing prevalence worldwide. This review will present recent evidence in support of this hypothesis and will discuss the underlying mechanisms and potential therapeutic targets. Altogether, findings presented here should help to better understand the mechanisms linking adiposity to depression and facilitate the identification of new preventive and/or therapeutic strategies.

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INTRODUCTION

Mental disorders account for almost 20% of the burden of disease worldwide, and they affect approximately 25% of the population during lifetime. Based on the Global Burden of Disease Study, depression is the most common of those disorders, representing the leading chronic condition and the first cause of years lived with disability (Whiteford *et al*, 2013). This disorder relates to a substantial increased risk of morbidity and death and is associated with a significant societal and economic burden. Although advances have been made in the treatment of depression, its prevalence is continuing to rise, notably owing to stagnation in the development of pharmacological treatments, the growth and aging of the population, and the increasing prevalence of chronic medical conditions, such as metabolic disorders and obesity, which are associated with an increased risk of

depressive comorbidity. This review will discuss the relevance of increased adiposity to the development of depression and the role of inflammation in promoting this effect.

FAT AND DEPRESSION: A VICIOUS CIRCLE

Obesity and depression currently represent substantial public health concerns, as the prevalence of these two conditions is growing worldwide. Albeit distinguishable in terms of etiopathological processes, mounting evidence suggests intricate bidirectional relationships between adiposity and depression (Luppino *et al*, 2010), which may explain their similar and parallel growth. Although depression relates to an increased risk of weight gain and obesity, overweight and obesity are in turn associated with a higher vulnerability for depressive disorders.

Economical changes together with modifications of lifestyle and diet habits represent potent contributors to the growing incidence of overweight and obesity worldwide. Primarily owing to an energy imbalance between calories consumed and calories expended, with an excessive consumption of energy-dense (high-fat and high-sugar) foods

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together with a reduction of physical activity, the pandemic of obesity is associated with a substantial economic burden and increasing medical costs (Hammond and Levine, 2010). In support of this, overweight and obesity are not only frequently associated with comorbidities and medical complications, including metabolic, endocrine, and cardiovascular diseases (CVD), but also neuropsychiatric disorders, such as depression (Dawes *et al*, 2016; Duarte-Guerra *et al*, 2015; Evans *et al*, 2005; Mather *et al*, 2009; Petry *et al*, 2008).

The incidence of depression in obese individuals is close to 30% (Dawes *et al*, 2016; Evans *et al*, 2005; Lasselin and Capuron, 2014a; Simon *et al*, 2008), a rate that is significantly higher than the one measured in the general population. Consistent with this, being obese was found to be associated with a risk of developing depression ranging from 1.18 to 5.25 depending on studies and methods of assessment (de Wit *et al*, 2010; Kasen *et al*, 2008; Ma and Xiao, 2010; Simon *et al*, 2008) and to predict recurrence of depressive episodes as well as antidepressant non-response in depressed patients (Kloiber *et al*, 2007; Nigatu *et al*, 2015; Oskooilar *et al*, 2009; Rizvi *et al*, 2014; Woo *et al*, 2016). Conversely, and supporting the bidirectional relationship between obesity and depression, the rates of obesity are particularly high in depressed patients, and depression was found to represent a strong predictor of weight gain and obesity, probably owing to effects of antidepressant medications and changes in eating behaviors and lifestyle (Lasserre *et al*, 2014; Lee *et al*, 2016; Simon *et al*, 2008). Moreover, psychosocial stress, a notorious risk factor for depression, is also known to contribute to weight gain and metabolic alterations and to participate in the development of obesity (Chuang *et al*, 2010; Kendler *et al*, 1999; Sinha and Jastreboff, 2013).

Usually greater in women (Carpenter *et al*, 2000; de Wit *et al*, 2010; Heo *et al*, 2006; Mitchell *et al*, 2012), depressive symptoms that develop in obese individuals often present atypical features such as increased appetite/weight gain, mood reactivity, and hypersomnia/fatigue (Chou and Yu, 2013; Levitan *et al*, 2012; Lojko *et al*, 2015). In agreement with this, overweight, obesity, and metabolic abnormalities, including leptin deregulation, appear to be more prevalent in atypical depression than in melancholic/typical depression (Chou and Yu, 2013; Cizza *et al*, 2012; Lamers *et al*, 2010; Lasserre *et al*, 2014; Levitan *et al*, 2012; Milaneschi *et al*, 2015). Interestingly, the association of atypical depression with leptin alterations was found to be stronger for increased adiposity levels (Milaneschi *et al*, 2015), pointing to a role for adiposity in this relationship. This finding also supports the hypothesis that depression with atypical features represents a metabolic subtype of depression likely related to adiposity (Lamers *et al*, 2010; Penninx *et al*, 2013). Moreover, and strengthening the notion of a bidirectional relationship between depression and obesity, atypical depression (notably through its association with increased appetite) is notorious for representing a significant risk factor for weight gain and obesity (Hasler *et al*, 2004).

In addition to atypical depression, bipolar depression was also found to be associated with adiposity and metabolic

variations (Alciati *et al*, 2007; Grothe *et al*, 2014; Vannucchi *et al*, 2014). Patients with bipolar disorders exhibit higher rates of obesity and metabolic comorbidities, which are believed to significantly modulate disease outcomes (Crump *et al*, 2013; McIntyre *et al*, 2010). Consistent with this, it was recently found that adiponectin levels represent potent moderators of illness course in bipolar depression, suggesting the involvement of metabolic processes in the physiopathology of the illness (Mansur *et al*, 2016). Interestingly, and supporting further the notion of specific associations with atypical depressive features, obesity in women with established type I bipolar disorder relates to episodes of major depression with atypical characteristics (Pickering *et al*, 2007).

As described for chronic diseases, the occurrence of depression in patients with obesity and metabolic disorders is associated with various deleterious consequences. Not only it substantially impacts quality of life but it also compromises weight loss and compliance to treatment or weight management strategies (Brunault *et al*, 2012; Dixon *et al*, 2003; Evans *et al*, 2005; Herva *et al*, 2006; Kinzl *et al*, 2006; Mazzeschi *et al*, 2012). Importantly, depressive comorbidities in obesity facilitate the development of additional complications, including CVD and metabolic disorders. These complications may occur together or mutually facilitate their co-occurrence, leading to the instauration of a vicious circle promoting the development of multiple disorders in chain. In support of this, obesity and metabolic disorders represent potent risk factors for CVD that, in turn, are associated with an increased vulnerability for depressive disorders (Almas *et al*, 2015; Hare *et al*, 2014). Similarly, depression, notably when it occurs in a context of metabolic disorders, is known to represent a significant risk factor for the development of CVD (Martin *et al*, 2016; Wulsin and Singal, 2003). These coexisting complications suggest the involvement of common pathophysiological mechanisms among which inflammation represents a key candidate given its position at the interface between metabolic, vascular, and central nervous system pathways and its pivotal role in the etiology of disorders affecting these systems (Figure 1).

IS INFLAMMATION LINKING FAT TO DEPRESSION?

Inflammation: A Main Feature of Obesity

Along with metabolic deregulations, basal systemic low-grade inflammation and enhanced susceptibility to immune-mediated diseases appear as a key component of obesity (Kanneganti and Dixit, 2012), which is now considered as an inflammatory condition affecting both the innate and acquired immune systems (Cancello and Clement, 2006; Gregor and Hotamisligil, 2011; Schmidt and Duncan, 2003). Increased plasma levels of inflammatory cytokines (including interleukin (IL)-1 β , tumor necrosis factor (TNF)- α , IL-6, and C-reactive protein (CRP)) and activation of inflammatory signaling pathways have been reported in both obese

Figure 1. Inflammation as a link between adiposity, depression and related comorbidities. The relationship between adiposity and depression is bidirectional, with adiposity being associated with an increased prevalence of depression, and in turn, depression (in particular, with atypical features) augmenting the risk of overweight/obesity. Depressive comorbidities in obesity facilitate the development of additional complications, including cardiovascular diseases (CVD), metabolic syndrome and type 2 diabetes. Inflammation represents the underlying link between adiposity and depression and their effects on comorbidities, given its position at the interface between metabolic, vascular and central nervous system pathways and its pivotal role in the etiology of disorders affecting these different systems.

individuals (Capuron *et al*, 2011b; Park *et al*, 2005; Visser *et al*, 1999) and animal models of obesity (Cani *et al*, 2008; De Souza *et al*, 2005; Dinel *et al*, 2011, 2014; Lawrence *et al*, 2012; Pistell *et al*, 2010; Xu *et al*, 2003).

Different complementary mechanisms contribute to the progressive development of chronic low-grade inflammation associated with obesity. One of the main protagonists is the white adipose tissue, as shown by findings reporting associations between circulating levels of cytokines and measures of central adiposity (Park *et al*, 2005; Visser *et al*, 1999). Conversely, weight loss, induced either by low-caloric diet or bariatric surgery, significantly reduces peripheral inflammation in obese individuals (Belza *et al*, 2009; Hakeam *et al*, 2009; Manco *et al*, 2007; Rao, 2012) and animals (Liu *et al*, 2014; Schneck *et al*, 2014; Zhang *et al*, 2011). Adipocytes, together with infiltrated macrophages and T cells that progressively accumulate in the white adipose tissue, have indeed the ability to potentially secrete inflammatory mediators (Cancello *et al*, 2006; Gregor and Hotamisligil, 2011; Kim *et al*, 2014; Lasselin *et al*, 2014b; Zeyda *et al*, 2011). Part of systemic inflammation in obesity also comes from other organs, in particular, the liver and muscles that are similarly infiltrated by activated immune cells (McNelis and Olefsky, 2014; Pedersen and Febbraio, 2012).

More recently, the gut microbiota has received increasing attention as an additional important player in the pathogenesis of obesity, particularly with regard to modulation of inflammation, energy metabolism, and body weight homeostasis (Cani *et al*, 2012; Cani *et al*, 2009; Finelli *et al*, 2014; Flint, 2011; Tehrani *et al*, 2012; Verdam *et al*, 2013).

Although the gut microbiota consists of thousands of different bacterial species, two bacterial phyla corresponding, respectively, to the Gram-negative *Bacteroidetes* and the Gram-positive *Firmicutes*, are dominant in both humans and mice (Eckburg *et al*, 2005; Ley *et al*, 2005). Interestingly, obese individuals have lower bacterial diversity than lean subjects (Armougom *et al*, 2009; Turnbaugh *et al*, 2009) and impaired *Bacteroidetes/Firmicutes* ratio (Armougom *et al*, 2009; Cani *et al*, 2009; Ley *et al*, 2005; Verdam *et al*, 2013). Moreover, these alterations are related to markers of local, systemic, and brain inflammation and corrected after weight loss (Aron-Wisniewsky *et al*, 2012; Bruce-Keller *et al*, 2015; Cani *et al*, 2008; Furet *et al*, 2010). In overweight/obese humans, low fecal bacterial gene richness is also associated with higher overall adiposity and systemic inflammation (Cotillard *et al*, 2013; Le Chatelier *et al*, 2013). Abnormal increase in gut permeability to bacteria and their products, as reported in obesity, further contributes to the onset and progression of systemic inflammation (Brun *et al*, 2007). Chronic intake of high-fat diet in mice has been indeed shown to induce metabolic endotoxemia (ie, increased plasma levels of lipopolysaccharide (LPS)). By activating systemic macrophages through the binding of LPS to its Toll-like receptor-4, this endotoxemia increases in turn the inflammatory state in obesity (Cani *et al*, 2008; Cani *et al*, 2009; Verdam *et al*, 2013). Conversely, reduced serum levels of an endotoxemia marker, the LPS-binding protein, are found after weight loss in obese individuals (Cani *et al*, 2008; Yang *et al*, 2014).

Abundant evidence supports immune-to-brain communication, with peripheral cytokines acting on the brain to induce local production of cytokines (Anisman *et al*, 2008; Dantzer *et al*, 2008). Consistent with this, recent data highlight increased inflammatory processes in the brain of obese individuals (Buckman *et al*, 2013; Rummel *et al*, 2010). This is particularly notable in the hypothalamus, where clinical indication of glial activation has been reported (Thaler *et al*, 2012). Enhanced hypothalamic inflammatory cytokine expression and activation of dependent signaling pathways have also been repeatedly found in diet-induced obesity (DIO) models, both in baseline conditions or following an immune challenge (Andre *et al*, 2014; Cai and Liu, 2012; De Souza *et al*, 2005; Gao *et al*, 2014; Kleinridders *et al*, 2009; Maric *et al*, 2014; Pohl *et al*, 2009; Zhang *et al*, 2008). Central inflammation in obesity likely results from adiposity-related systemic inflammatory processes or endotoxemia induced by impaired gut permeability, as discussed above. This last assumption fits with mounting literature reporting the existence of a rich and complex communication network between the gut and the brain that involves endocrine, immune, and neural pathways (Grenham *et al*, 2011). Of note, the possibility that central inflammation may, on the contrary, represent an early event promoting the development of obesity following high-fat diet exposure cannot be excluded. Supporting this notion, blocking hypothalamic inflammation prevents high-fat diet-induced obesity and related metabolic alterations

(Milanski *et al*, 2009; Zhang *et al*, 2008). In addition, prenatal cytokine exposure has been shown to promote the development of obesity at adulthood (Dahlgren *et al*, 2001). Whatever the case, it is now clear that increased hypothalamic inflammation is related to the metabolic deregulations that characterize severe obesity, including leptin resistance, insulin resistance, and hyperglycemia (De Souza *et al*, 2005; Kleinridders *et al*, 2009; Velloso *et al*, 2008; Zhang *et al*, 2008). By impairing hypothalamic peptidergic neuronal networks involved in the control of food intake and energy balance, inflammatory factors may also promote weight gain (Thaler and Schwartz, 2010; Velloso *et al*, 2008). Similar effects have been reported following chronic psychosocial stress, which induces both inflammation and metabolic alterations, including weight gain (Bierhaus *et al*, 2003; Chuang *et al*, 2010; Kleinridders *et al*, 2009). Interestingly, obesity-associated inflammation, notably as it relates to the visceral adipose tissue, was found to impact obesity treatment outcomes, with increased adipose expression of immune cells and inflammatory markers being associated with lower BMI reduction after bariatric surgery in severely obese patients (Lasselin *et al*, 2014b).

In addition to the hypothalamus, the hippocampus and cortex also display signs of neuroinflammation in rodent models of obesity (Dinel *et al*, 2011, 2014; Erion *et al*, 2014; Pistell *et al*, 2010). For example, increased systemic inflammation and/or reduced immune competence, which are reported in genetic models of severe obesity (*ob/ob* (deficient for leptin) and *db/db* (deficient for functional leptin receptor) mice), are associated with increased hippocampal cytokine expression (Dinel *et al*, 2011, 2014; Erion *et al*, 2014). Similarly, exacerbated hippocampal inflammation has been reported in DIO models (Andre *et al*, 2014; Boitard *et al*, 2014; Dinel *et al*, 2014). Consistent with these findings, clinical evidence shows an inverse association between activation of inflammatory processes and brain volume, notably in the hippocampus and prefrontal cortex (Meier *et al*, 2016; Savitz *et al*, 2014; Zunszain *et al*, 2012), and between brain volume and waist circumference and/or BMI (Janowitz *et al*, 2015; Pannacciulli *et al*, 2006; Yokum *et al*, 2012).

Neuropsychiatric Effects of Inflammation: Evidence and Mechanisms

Over the past decades, the key role of deregulated production and/or brain action of cytokines in the induction of neuropsychiatric disorders has been abundantly documented (Capuron and Miller, 2011a; Dantzer *et al*, 2008; Lasselin and Capuron, 2014a). Cytokines, released locally by activated innate immune cells in conditions of tissue injury, infection, or inflammation, are able to act systemically on distant organs, including the brain that they can reach through several non-exclusive humoral, neural, and cellular pathways, as reviewed elsewhere (Capuron and Miller, 2011a; Dantzer *et al*, 2008). Activation of immune-to-brain communication ultimately induces the production of brain

cytokines by activated endothelial and glial cells, particularly microglia (Castanon *et al*, 2004; Laye *et al*, 1994; Ransohoff and Perry, 2009). Locally produced inflammatory cytokines activate the neuroendocrine system (in particular, the hypothalamic–pituitary–adrenal (HPA) axis), impair neurotransmitter metabolism and function, and alter neural plasticity and brain circuitry. These alterations, in turn, lead to a large number of behavioral changes (including weakness, listlessness, malaise, anorexia, fatigue and transient cognition and mood alterations) collectively referred to as sickness behavior and contributing to host defense (Capuron and Miller, 2011a; Dantzer *et al*, 2008). This adaptive behavioral response is supposed to be strictly tailored to the stimulus and time-limited. However, it can sometimes become abnormal and trigger neuropsychiatric symptoms, in particular when brain inflammation remains chronically activated or badly regulated (Borsini *et al*, 2015; Dantzer *et al*, 2008). Most evidence supporting these findings comes from clinical studies involving patients receiving cytokines, in particular interferon (IFN)- α , as treatment for cancers or hepatitis C. Although they are free of any psychiatric antecedent, up to 45% of these patients develop major depression during IFN- α therapy, unless they receive a prophylactic antidepressant treatment (Capuron *et al*, 2002; Musselman *et al*, 2001).

A large set of clinical and preclinical data suggest that cytokine-induced depression may rely on impairment of monoaminergic neurotransmission (particularly, serotonin, glutamate, and dopamine), likely owing to inflammation-induced activation of specific enzymes in activated monocytes, macrophages, and brain microglia (Capuron and Miller, 2011a; Capuron *et al*, 2011c; Dantzer *et al*, 2008) (Figure 2). One of these enzymes is GTP-cyclohydrolase 1 (GTP-CH1) (Felger and Miller, 2012; Haroon *et al*, 2012), which produces neopterin at the expense of tetrahydrobiopterin, or BH4, a co-factor essential for dopamine and serotonin biosyntheses (Capuron *et al*, 2011c; Murr *et al*, 2002; Oxenkrug *et al*, 2011). Consistent with the hypothesis that inflammation-induced alterations in the GTP-CH1 pathway contributes to the development of neuropsychiatric symptoms, reduced BH4 levels are reported in patients with psychiatric disorders (Hashimoto *et al*, 1994; Hoekstra *et al*, 2001). Similarly, increased blood neopterin concentrations correlate with a higher number of depressive episodes in patients with major depression (Celik *et al*, 2010). In addition, fatigue, decreased motivation, and anhedonia in IFN- α -treated patients and non-human primates correlate with significant alterations in BH4 (Felger *et al*, 2013) and dopamine metabolism/function (Capuron *et al*, 2012). GTP-CH1 activation also impairs nitric oxide synthase (NOS) activity, leading to generation of free radicals and oxidative stress and reducing BH4 availability by promoting its oxidation. Akin with this, systemic administration of IFN- α decreases the brain levels of dopamine and BH4 in rats through a mechanism involving NO, as this effect is reversed by treatment with an NOS inhibitor (Kitagami *et al*, 2003).

Figure 2. Inflammation induces alterations in monoamine biosynthesis. Alterations in adipose tissue and gut microbiota lead to the production of inflammatory factors and endotoxemia, thus promoting a state of chronic low-grade inflammation. Inflammatory factors activate GTP-cyclohydrolase-1 (GTP-CH1), leading to the production of neopterin at the expense of tetrahydrobiopterin (BH4) and reducing activity of the enzymes tyrosine hydroxylase (TH) and tryptophan hydroxylase (TPH) involved in dopamine and serotonin syntheses. In addition, lower level of BH4 reduces nitric oxide synthase (NOS) activity and increased O_2 concentration, which exacerbates BH4 inhibition. Cytokines also activate the enzyme indoleamine 2,3-dioxygenase (IDO), which results in the degradation of tryptophan along the kynurenine pathway at the expense of serotonin. Kynurenine is then degraded into quinolinic acid in microglia, thus promoting neurotoxicity.

Another enzyme also activated by cytokines and whose involvement in inflammation-induced neuropsychiatric symptoms has been well documented is the indoleamine 2,3-dioxygenase (IDO). This enzyme is the first and rate-limiting enzyme degrading tryptophan, the essential amino-acid precursor of serotonin, along the kynurenine pathway (Dantzer *et al*, 2008; O'Connor *et al*, 2009b; O'Connor *et al*, 2009c). By consuming tryptophan, IDO activation can therefore, in turn, reduce the synthesis of serotonin. Association of neuropsychiatric symptoms with increased kynurenine levels or altered kynurenine/tryptophan ratio has been demonstrated in several conditions associated with inflammation, including IFN- α -treated patients, aging, or Alzheimer's disease (Capuron *et al*, 2011c; Gulaj *et al*, 2010; Forrest *et al*, 2011; Gold *et al*, 2011; Raison *et al*, 2010). Microglial activation of the kynurenine pathway can also ultimately lead to the production of neuroactive glutamatergic compounds, including 3-hydroxykynurenine and quinolinic acid, which have a key role in neuronal death by stimulating NMDA receptors and promoting oxidative stress (Campbell *et al*, 2014; Dantzer and Walker, 2014; Stone *et al*, 2012). In support of this notion, brain or cerebrospinal fluid concentrations of kynurenine neurotoxic metabolites are elevated in several neuropsychiatric or neurodegenerative diseases (Campbell *et al*, 2014; Schwarcz *et al*, 2001; Steiner *et al*, 2011; Stone *et al*, 2012) and have been related to the stretch of brain damages, impaired neurogenesis, and development of neuropsychiatric symptoms (Savitz *et al*,

2015a; Savitz *et al*, 2015b; Stone *et al*, 2012; Zunszain *et al*, 2012). In line with clinical findings, preclinical studies performed in rodents treated with an immune challenge have documented associations between emotional/cognitive alterations and both peripheral and brain IDO activation (Andre *et al*, 2008; Corona *et al*, 2013; Frenois *et al*, 2007; Gibney *et al*, 2013; Lawson *et al*, 2013; Lestage *et al*, 2002; Moreau *et al*, 2005, 2008; Salazar *et al*, 2012; Xie *et al*, 2014). In addition, aged mice or mice with constitutive microglial overactivation display, upon immune challenge, sustained cytokine production together with protracted brain IDO expression and depressive-like behavior (Corona *et al*, 2010; Godbout *et al*, 2008; Kelley *et al*, 2013). More importantly, pharmacological or genetic inhibition of IDO prevents the development of depressive/anxiety-like behaviors and cognitive impairments (Barichello *et al*, 2013; Henry *et al*, 2009; O'Connor *et al*, 2009a; O'Connor *et al*, 2009b; O'Connor *et al*, 2009c; Salazar *et al*, 2012; Xie *et al*, 2014). Conversely, systemic kynurenine administration dose-dependently impairs emotional behaviors and spatial memory (Alexander *et al*, 2012; Chess *et al*, 2009; O'Connor *et al*, 2009c; Salazar *et al*, 2012). Of note, blockade of NMDA receptors inhibits the induction of depressive-like behavior by an immune challenge (Walker *et al*, 2013), whereas mice deficient for IDO are protected against NMDA receptor-mediated excitotoxicity (Mazarei *et al*, 2013). Altogether, these results point to a pivotal role of inflammation-induced impairment of brain neurotransmission and/or promotion of

neurotoxicity in mediating the development of neuropsychiatric symptoms in inflammatory conditions.

INFLAMMATION IN DEPRESSIVE COMORBIDITIES OF OBESITY

Clinical and Experimental Evidence

Growing evidence suggests that obesity-related inflammation has a central role in the development of depressive comorbidities (Castanon *et al*, 2014; Lasselin and Capuron, 2014a). At the clinical level, significant associations between elevated levels of inflammatory mediators (eg, CRP, IL-6, and leptin) and depressive symptoms have been documented in individuals suffering from obesity or the metabolic syndrome (Capuron *et al*, 2008; Chirinos *et al*, 2013; Dixon *et al*, 2008; Ladwig *et al*, 2003). Moreover, in patients with the metabolic syndrome, systemic low-grade inflammation was found to represent a major determinant of depressive symptoms (Capuron *et al*, 2008). More recently, it was shown that CRP levels explain approximately 20% of the increase in depression scores over time in obese subjects (Daly, 2013). Consistent with the role of adiposity in these associations, reductions in levels of inflammatory markers after bariatric surgery-induced weight loss correlate with significant improvements in the emotional status and depressive symptoms of obese individuals (Capuron *et al*, 2011b; Emery *et al*, 2007). In addition, severely obese individuals have been found to display lower circulating tryptophan levels together with greater kynurenine levels in comparison to lean controls, consistent with inflammation-driven activation of IDO pathway (Brandacher *et al*, 2007). A shift toward activation of the enzymatic pathway leading to the production of kynurenine neurotoxic metabolites was also demonstrated in obese patients (Favennec *et al*, 2015). Interestingly, the recent finding that adipokines with potent anti-inflammatory properties (eg, adiponectin) have a role in the antidepressant effects of the NMDA receptor antagonist ketamine further supports the notion that inflammation-induced alterations of glutamatergic neurotransmission may contribute to the development of obesity-related depressive comorbidities (Machado-Vieira *et al*, 2016). Although activation of the kynurenine pathway has been primarily reported to represent a key component in the initiation and propagation of obesity and related medical complications, including CVD and the metabolic syndrome (Mangege *et al*, 2014), it is thus also possible that it contributes to the development of depressive comorbidities, notably through neurotoxic effects of kynurenine metabolites. The hippocampal atrophy found in obese subjects in comparison with healthy controls is in favor of this assumption (Fotuhi *et al*, 2012).

In line with clinical findings, recent preclinical studies have started to describe the causality of events and to identify some underlying mechanisms. The occurrence of behavioral (mood and cognitive) symptoms in DIO models or genetically obese rodents (*db/db*) was found to be associated

with higher hippocampal and cortical expression of inflammatory cytokines (Castanon *et al*, 2015; Dinel *et al*, 2011, 2014; Erion *et al*, 2014; Kanoski and Davidson, 2011; Pistell *et al*, 2010). Interestingly, hippocampal IL-1 β expression in obese *db/db* mice is related to adiposity and its blockade prevents cognitive impairment by normalizing dendritic spine density and local synaptic dysfunction (Erion *et al*, 2014). Of note, *db/db* mice also display association between hippocampal microglial activation and obesity-related elevation in plasma glucocorticoids (Dey *et al*, 2014). Similarly, DIO mice display exacerbated HPA axis activation in response to an immune challenge, together with increased neuroinflammation and depressive-like behavior (Andre *et al*, 2014). These results support the notion that inflammatory factors and HPA axis, which are tightly interrelated and highly activated in obesity (Dinel *et al*, 2011, 2014), may act together in that context to promote mood alterations (Dey *et al*, 2014; Hryhorczuk *et al*, 2013; Stranahan *et al*, 2008). Both cytokines and glucocorticoids have been shown to impair hippocampal neurogenesis and neuronal function in obese mice (Dinel *et al*, 2011; Erion *et al*, 2014; Stranahan *et al*, 2008; Wosiski-Kuhn *et al*, 2014). Moreover, behavioral alterations reported in obese animals are linked to increased inflammation and reduced levels of the neurotrophic factor BDNF in the cortex and hippocampus (Dinel *et al*, 2011; Pistell *et al*, 2010), whereas normalization of hippocampal BDNF levels prevents hippocampus-mediated cognitive impairments (Kariharan *et al*, 2015; Moy and McNay, 2013).

Taken together, these results point to a link between increased neuroinflammation, impaired neurogenesis/synaptic plasticity, and behavioral alterations in obesity. Supporting the implication of brain kynurenine pathway activation in these processes, an association was recently found between the amplitude of brain IDO activation and the development of depressive-like behavior in obese mice challenged with LPS (Andre *et al*, 2014; Dinel *et al*, 2014). Activation of GTP-CH1, as reflected by increased circulating levels of neopterin, has also been reported in obese rats (Finkelstein *et al*, 1982) and patients (Ledochowski *et al*, 1999; Oxenkrug *et al*, 2011; Oxenkrug, 2010). These data suggest that this activation, and the consequent alteration of dopamine neurotransmission, may also contribute to the development of neuropsychiatric symptoms in obesity. Although this assumption still needs to be confirmed, it is supported by several reports documenting impaired dopamine function together with alterations in basal ganglia and reward circuitry in obese patients (de Weijer *et al*, 2011; Volkow *et al*, 2011; Wang *et al*, 2001). Moreover, depressive-like behavior is associated with alterations in striatal circuitry in DIO mice, further supporting a role for dopamine-related disruptions in obesity-associated depressive symptoms (Sharma and Fulton, 2013). Finally, it is worth mentioning that, in addition to the different pathways discussed above, alterations of the gut-brain axis may represent another mechanism of inflammation-driven neuropsychiatric comorbidities, given the role of this axis in the

development of neuropsychiatric symptoms after chronic stress (Cryan and Dinan, 2012; Grenham *et al.*, 2011). The recent finding that gut microbiota transplantation from obese to lean mice is able to induce neurobehavioral changes in the absence of obesity supports this notion (Bruce-Keller *et al.*, 2015). Altogether, these data point to brain inflammation as a major player in the development of obesity-related neuropsychiatric symptoms and start to highlight the participation of several pathways/systems that are not necessarily specific to the condition of obesity but that can still modulate or relay the brain impact of inflammatory processes.

Role of Insulin Resistance

Among the pathways by which inflammation may promote the development of neuropsychiatric comorbidities, insulin resistance, which is a trademark of severe obesity and the metabolic syndrome, deserves to receive special attention. Insulin, whose circulating levels and signaling pathway are altered in obesity, is able to interact with inflammatory processes and to act at the periphery and within the brain, in particular, in the hypothalamus, to control energy expenditure, glucose homeostasis, and feeding behavior (Hemmati *et al.*, 2014; Hotamisligil, 2006; Velloso *et al.*, 2008). Systemic inflammation resulting from the recruitment of macrophages in adipose tissue and pancreatic islets reported in obesity has been shown to impact β -cell secretory function and survival, reducing in turn insulin secretion and initiating insulin resistance (Donath and Shoelson, 2011; Hotamisligil, 2006). From a molecular perspective, inflammatory cytokines (in particular, IL-1 β and TNF- α) have been shown to impair signaling of the insulin receptor both at the periphery and within the brain (De Souza *et al.*, 2005; Hotamisligil, 2006; Lann and LeRoith, 2007; Xu *et al.*, 2003). Reciprocally, emerging evidence suggests that insulin may display anti-inflammatory properties by preventing hyperglycemia and modulating key inflammatory molecules (for reviews, see Hyun *et al.*, 2011; Scheen *et al.*, 2015). Interestingly, recent reports on brain location of insulin receptors and their link with neuronal function and mood have introduced new ways of considering this hormone, in particular, regarding its potential role in obesity-related neuropsychiatric symptoms (Blazquez *et al.*, 2014; Ghasemi *et al.*, 2013a). In support of this notion, converging findings reveal dysfunctions of insulin signaling pathway in different neurological or neuropsychiatric disorders (Blazquez *et al.*, 2014; Ghasemi *et al.*, 2013b; Yates *et al.*, 2012). A number of epidemiological studies also point to an association between medical conditions defined by insulin resistance and depression (Cline *et al.*, 2012; Kan *et al.*, 2013; Pomytkin *et al.*, 2015). In addition, insulin resistance displayed by obese *db/db* mice in brain areas with high density of insulin receptors, such as the hippocampus and cortex, is associated with emotional alterations (Dey *et al.*, 2014; Kim *et al.*, 2011). Conversely, compounds enhancing neuronal insulin receptor-mediated transmission in the hippocampus show antidepressant-like

effects in preclinical paradigms of depression (Cline *et al.*, 2012; Cline *et al.*, 2015). In line with these findings, recent pharmacological studies highlight the antidepressant properties of several antidiabetic drugs, which may involve, beyond improvement of hyperglycemia, positive impact on inflammation and neuronal activity (Gupta *et al.*, 2014; Pomytkin *et al.*, 2015). Consistent with this, normalizing hyperglycemia in *db/db* mice does not improve anxiety-like behavior or spatial memory deficits (Stranahan *et al.*, 2008; Stranahan *et al.*, 2009), whereas these are improved by reducing hippocampal inflammation (Erion *et al.*, 2014). Moreover, treating hyperglycemic mice with the antidiabetic drug, extendin-4, has been recently shown to improve cognitive dysfunction by reducing hippocampal inflammation (Huang *et al.*, 2012). Altogether, these data are in favor of the involvement of inflammation-related complex non-exclusive pathophysiological processes in the development of neuropsychiatric symptoms in obesity. This notion is comforted by data indicating that the risk of depressive symptoms in obese individuals is increased in metabolically unhealthy obesity, ie, when adiposity is associated with greater inflammation and metabolic abnormalities (Jokela *et al.*, 2014).

FUTURE RESEARCH DIRECTIONS

Given the alarming and continuous rise in depressive disorders and obesity, their intricate relationship and their additive role as risk factors for many other medical complications, multiple efforts have been carried out over the past decades to identify preventive and/or therapeutic strategies aiming at reducing their health and economic impact. The complex and bidirectional relationships existing between increased adiposity and depressive disorders emphasize common pathophysiological mechanisms. As illustrated by both clinical and preclinical evidence reported in this review, these mechanisms seem to converge on inflammatory processes and related alterations of neuroendocrine and neurotransmitter pathways, which are a trademark of both disorders. Inflammation appears therefore to be the cornerstone of the different factors contributing to link depressive disorders and obesity (Figure 3). In that context, strategies to reduce inflammation, either pharmacological or non-pharmacological, may help in the prevention and management of obesity-related neuropsychiatric comorbidity and improve quality of life and health outcomes in patients afflicted with these conditions.

Pharmacological Strategies

Anti-inflammatory treatments that may be relevant for the prevention and management of depressive disorders occurring in conditions of overweight, obesity, or metabolic disorders may target either directly inflammatory signaling pathways or indirectly the enzymatic pathways that are modulated by inflammation. In particular, the administration of anticytokines, including the monoclonal antibody against TNF- α , infliximab, may represent a useful strategy.

Figure 3. Overview of the mechanisms and pathways of adiposity-driven inflammation in depressive morbidity. Overweight/obesity is associated with low-grade inflammation originating from the adipose tissue and changes in gut microbiota composition. Immune-to-brain communication leads to the activation of brain inflammatory processes responsible for substantial changes in brain function, including alterations in neurotransmitter biosynthesis and changes in neurogenesis and synaptic plasticity. Concomitantly, brain cytokines promote neurotoxicity through activation of glutamate pathways. Altogether, these alterations contribute to the development of depressive symptoms. BH4: tetrahydrobiopterin; GTP-CH1: guanosine triphosphate cyclohydrolase-1; IDO: indoleamine 2,3-dioxygenase; LPS: lipopolysaccharide.

In support of this notion, infliximab was found to reduce depressive symptoms in rodent models of depression (Karson *et al*, 2013; Liu *et al*, 2015) as well as in humans suffering from major depression and exhibiting higher level of circulating CRP (Raison *et al*, 2013). Interestingly, these patients were also those who exhibited higher BMI. These promising findings highlight the necessity of clearly identifying, in future studies, the subgroups of depressed patients who could benefit from such treatment, in particular, by taking into account their metabolic and inflammatory profiles. Beyond cytokines themselves, antidepressant-like effects have been recently reported in obese mice after pharmacological blockade of cyclooxygenase-2, an enzyme activated by cytokines (Kurhe *et al*, 2014). On the other hand, the opportunity of blocking other enzymatic targets of cytokines, in particular, those involved in the kynurenine pathway whose activity increases with adiposity (Favennec *et al*, 2015) and correlates with depressive symptoms in both obese individuals and animals, likely represents another interesting therapeutic approach, as recently suggested from findings in diabetic rats (da Silva Dias *et al*, 2015). Alternatively, targeting the neopterin pathway, in particular, BH4, which is a critical cofactor for monoamine synthesis

and is altered in obesity (Finkelstein *et al*, 1982; Ledochowski *et al*, 1999; Oxenkrug *et al*, 2011; Oxenkrug, 2010), may also provide a useful way to reduce adiposity-driven inflammation and related depressive symptoms. This assumption is supported by findings reporting relief of treatment refractory depression by BH4 replacement (Curtius *et al*, 1983; Pan *et al*, 2011). Finally, owing to the tight interactions between inflammation and metabolic alterations, including insulin resistance and dyslipidemia, adiposity-driven inflammation may also be targeted by antidiabetic drugs, which have already been shown to display antidepressant properties (Gupta *et al*, 2014; Pomytkin *et al*, 2015; Scheen *et al*, 2015). Similarly, recent clinical evidence indicates that the anti-dyslipidemia drugs, statins, which also display anti-inflammatory properties, improve the efficacy of antidepressant treatment when administered as adjuvant therapy (Köhler *et al*, 2016; Salagre *et al*, 2016).

Non-Pharmacological Interventions

Non-pharmacological interventions, including weight loss programs and nutritional approaches, may be of particular interest to lower inflammation and consequently improve

mental health in individuals with obesity and comorbid depressive symptoms. In support of this notion, sustained weight loss, induced by low-calorie diet or bariatric surgery, was found to potently regulate inflammation (Bastard *et al*, 2000; Belza *et al*, 2009; Capuron *et al*, 2011b; Clement *et al*, 2004) and to improve depressive symptoms in obese individuals (Brinkworth *et al*, 2009; Capuron *et al*, 2011b; Dawes *et al*, 2016; Dixon *et al*, 2003; Dixon *et al*, 2008). Similarly, exercise, which promotes weight loss and maintenance, stimulates the production of muscular cytokines with anti-inflammatory properties (Peake *et al*, 2015; Pedersen *et al*, 2007) and was found to possess antidepressant effects comparable to antidepressant medication (Blumenthal *et al*, 2007; Dunn *et al*, 2005).

In addition, nutritional interventions based on factors with immunomodulatory properties and known impact on behavior and mood appear as tractable strategies for developing novel therapeutics for obesity-related neuropsychiatric disorders. These strategies not only include the use of omega-3 polyunsaturated fatty acids (n-3 PUFA) and antioxidants (for reviews, see Bazinet and Laye, 2014; Gomez-Pinilla and Nguyen, 2012) but also compounds that beneficially alter the microbiota (eg, prebiotics or probiotics) (Cryan and Dinan, 2012). Relevant to the role of inflammation in promoting effects of nutritional interventions on depressive symptoms, the n-3 PUFA eicosapentaenoic acid (EPA) was recently found to be effective in the prevention of IFN- α -induced depression in hepatitis C-infected patients (Su *et al*, 2014). In addition, a recent report indicates that patients with major depression and high level of systemic inflammation, which highly correlates with increased BMI, are more likely to respond to EPA treatment than depressed subjects with low inflammation (Rapaport *et al*, 2016). These findings support the hypothesis that nutritional intervention with EPA n-3 PUFA may be of particular relevance for improving depressive symptoms in obese individuals. Alternatively, the opportunity of targeting enzymatic pathways activated by cytokines and altering mood (eg, IDO/BH4 pathways) with amino-acid-based compounds also deserves to be considered.

CONCLUSIONS

Depression and overweight/obesity currently represent important public health concerns given their increasing prevalence worldwide, their societal burden, and their substantial impact on health and morbidity. Recent evidence highlights an intricate relationship between depression and obesity and suggests that the pandemic of overweight/obesity may contribute to the increased prevalence of depression. Findings discussed in the present review point to inflammation as a pivotal and crucial mediator of the relationship between adiposity and depression. The implication of such findings may contribute to the identification of novel targets for a better prevention and treatment of depression in chronic medical conditions associated with increased

inflammatory processes, such as overweight/obesity and metabolic disorders.

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