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Review article

Pathways linking obesity to neuropsychiatric disorders

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ABSTRACT

Obesity has been associated with cognitive and behavioral syndromes. Individuals who are obese have higher risk for developing neuropsychiatric disorders such as depression and dementia than non-obese. Conversely, patients with neuropsychiatric conditions may exhibit some features that contribute to obesity development such as unhealthy behaviors and treatment with drugs that increase appetite. This review addresses the multiple pathways implicated in the relationship between obesity and neuropsychiatric disorders, mainly mood disorders, schizophrenia, and major neurocognitive disorder or dementia. Both obesity and neuropsychiatric disorders are characterized by a low-grade systemic inflammation and neuroinflammation. Obesity is frequently accompanied by neuroendocrine changes, particularly involving the hypothalamic–pituitary–adrenal (HPA) axis. Indeed, activation of the stress system is commonly seen as a trigger for mood episodes, psychosis exacerbation, and cognitive decline. Growing evidence suggests the role of gut microbiota in obesity and brain functioning through the modulation of the inflammatory response and HPA axis. Owing to the intricate relationship between obesity and neuropsychiatric disorders, tackling one of them may affect the other. Therefore, a better understanding of the pathways underlying the link between obesity and neuropsychiatric disorders can contribute to the development of therapeutic strategies for these conditions.

Introduction

Neuropsychiatric disorders, including mood and cognitive disorders, are an important cause of impairment, representing a major global burden accounting for >20% of years lived with disability worldwide [1]. People with mood disorders exhibit more unhealthy behaviors such as smoking, physical inactivity, and excessive alcohol consumption, which are associated with obesity, than those without mood disorders [2]. Obesity is an established risk factor for mood disorders.

According to Strine et al., individuals who are obese have a 60% greater chance of developing depression than non-obese people [2]. Similarly, cognitive functioning seems to be influenced by obesity [3–5]. For instance, midlife obesity may increase the risk for dementia later in life [6]. Obese adolescents showed worse cognitive performance in tests assessing attention and mental flexibility than their non-obese peers [7]. Moreover, weight loss induced by bariatric surgery or diet restriction has been associated with improvements in mood and cognition [8]. The context of bariatric surgery is very complex from a neuropsychiatric perspective and is beyond the scope of this review. Candidates for bariatric surgery have increased frequency of psychiatric disorders, suggesting that individuals with severe obesity may be more prone to develop these conditions [9,10]. Actually, depressive symptoms are very likely to return 24 mo after bariatric surgery [9].

This review addressed the intricate relationship between obesity and neuropsychiatric disorders, focusing on mood disorders, schizophrenia, and major neurocognitive disorder or dementia. This link seems to involve multiple biological pathways, including the inflammatory or immune system, hypothalamic–pituitary–adrenal (HPA) axis, and the gut–brain axis, that must be seen as potential therapeutic targets for both obesity and neuropsychiatric conditions.

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Mood disorders and obesity

Mood disorders comprise a heterogeneous group of conditions marked by the emergence of clinically significant symptoms expressed during depressive (sadness, anhedonia, abulia) or manic (euphoria, irritability) episodes. Although major depressive disorder is defined by the presence of recurrent or persistent depressive episodes (or depression), bipolar disorders are defined by the presence of mania (bipolar I) or hypomania (bipolar II) that can alternate with depressive episodes. The 12-mo prevalence of major depressive disorder is around 6%, and ~2.4% of people worldwide have bipolar disorders [11,12].

The relationship between obesity and depression is bidirectional. Individuals who are obese have a higher risk for developing depression than non-obese people. Obesity may influence the person's self-image with a self-depreciating perception, leading to depressive symptoms, especially in the context of high social expectations and beauty standards [13]. Conversely, depressive symptoms can contribute to the development of obesity owing to an unhealthy lifestyle, including sedentarism and eating habits [2,14]. Moreover, food preference may change during periods of stress or depression. For instance, Ansari et al. showed a positive correlation between depressive symptoms and unhealthy food consumption, including sweets, cookies, snacks, and fast food among college students [15]. Mood disorders can also lead to carbohydrate-craving and increases in sweet or starchy food intake [16,17]. In fact, meals with high-carbohydrate content can temporarily lift the mood, particularly because consumption of highly palatable food activates the brain opioid system, producing hedonic responses [16]. Blocking the opioid response with naloxone, an opioid receptor antagonist, reduces the consumption of high-fat sweet foods in binge eaters, whereas individuals exposed to opioid agonists prefer high-sugar foods [18,19]. In addition, alternative mechanisms explaining how carbohydrates may affect mood have implicated alteration of motivational drive, and serotonergic and stress response systems. The consumption of carbohydrates may increase serotonin production in the brain owing to increased tryptophan availability [17].

Mood disorders are also characterized by sleep abnormalities, with insomnia affecting approximately three-fourths of patients with depression and decreased need for sleep being a hallmark of hypo/mania [20]. Given that sleep is a major regulator of neuroendocrine functions, sleep impairment is associated with dysfunction of glucose metabolism, an increase in ghrelin levels (orexigenic hormone), a decrease in leptin levels (anorexigenic hormone), and consequently, increase in hunger [21]. Together, these behavioral and neurobiological mechanisms may increase the risk for obesity in patients with depression.

Around 70% of patients with bipolar disorder are overweight or obese, and this is primarily associated with the duration of depressive episodes [12,22]. Although bipolar disorders are defined by the presence of mania or hypomania, depressive symptoms or episodes are more frequent, playing a major role in the prognosis of these patients. Accordingly, the aforementioned comments on depression also apply to patients with bipolar disorder. Conversely, during mania or hypomania, patients tend to eat less and to be physically overactive [23]. It is worth emphasizing that many antidepressants (e.g., mirtazapine and tricyclic antidepressants) and mood stabilizers, mainly valproate and lithium, are associated with weight gain. According to a recent cohort study, the use of antidepressant drugs contributes to weight gain mainly during the second and third years of treatment [24]. Although the mechanisms underlying antidepressant-related weight gain are not fully understood [25], involving antihistaminic effect among others, it is very important to consider the metabolic consequences of antidepressant treatment.

Schizophrenia and obesity

Schizophrenia is a severe psychiatric disorder characterized by psychotic symptoms (hallucinations and delusions), negative symptoms (avolition, flat affect, social withdrawal), and cognitive dysfunction [26]. The prevalence of obesity and overweight among patients with schizophrenia is higher than in the general population [27]. Several factors contribute to weight gain in this population, including sedentary lifestyle, unhealthy eating behaviors, and notably, the use of antipsychotics [28]. A recent systematic review showed that patients with schizophrenia also engage in significantly less moderate and vigorous physical activity than healthy controls [29].

The initiation of antipsychotic treatment by drug-naive patients usually leads to significant weight gain of around 4 kg or 1.2 points in the body mass index (BMI) within the first 12 wk [30]. Most antipsychotics are associated with weight gain, but the effect is more pronounced with several second-generation antipsychotics, particularly olanzapine and clozapine [27]. The mechanisms underlying this drug-induced weight gain involve appetite increase and changes in eating preference. Olanzapine seems to increase the preference for high-fat and high-sugar diets, an effect possibly related to olanzapine-induced plasma glucagon-like peptide-1 decrease [31]. Glucagon-like peptide-1 plays a role in satiation signals and modulation of taste sensitivity [31–33].

The poor diet quality of patients with schizophrenia has also been systematically described [34]. Patients' diet is usually characterized by a high consumption of saturated fat and low intake of fruit and dietary fiber [34]. Increases in orexigenic protein expression (neuropeptide Y), decreases in anorexigenic protein expression, and upregulation of ghrelin signaling have been proposed as the mechanisms for this unhealthy food preference in schizophrenia [27].

The net effect of these changes is a high risk for metabolic syndrome and, as consequence, the development of chronic metabolic diseases such as type 2 diabetes [31]. The elevated prevalence of metabolic complications in schizophrenia not only influences the quality of life of these patients, but also decreases their life expectancy by an estimated 15 y [35]. Accordingly, strategies aiming to treat obesity and metabolic complications in these patients may have a positive effect on their prognosis.

Dementia and obesity

Dementia is a neuropsychiatric syndrome marked by progressive cognitive decline (e.g., memory, language, visuospatial skills, decision making, etc) that affects the functioning of the those affected [36]. Alzheimer's disease, pathologically defined by the accumulation of β-amyloid plaques and neurofibrillary tangles in cortical regions, is the main cause of dementia, followed by vascular dementia and other forms of neurodegenerative dementias [37]. Based on current estimates, it is expected that by 2050, worldwide numbers of individuals with dementia will reach 131.5 million [38].

Gustafson et al. were the first to suggest the association between dementia risk, particularly Alzheimer's disease, and BMI in women. In a cohort study involving 392 non-demented individuals followed for 18 y (from age 70 to 88 y), women who developed dementia had higher BMI than those without dementia [39]. Other epidemiologic studies have confirmed the association between midlife BMI and dementia. A meta-analysis carried out by Pedditizi et al. showed that obesity increases the risk for dementia 1.4-fold [6].

In line with these findings, in a recent study with 1 349 857 adults without dementia from 39 cohorts in Europe, the United States, and Asia, higher BMI, measured >20 y earlier, was associated with increased dementia risk. However, higher BMI 10 y before the diagnosis of dementia was associated with a decreased risk for dementia [40]. This phenomenon of reversing the direction of association between BMI and dementia has also been reported by other studies [41–44].

In other words, studies based on traditional anthropometric measures, such as weight and waist circumference, have reported that high BMI and central obesity in midlife may increase the risk for dementia later in life. After midlife, however, decreases in BMI are frequently observed in association with dementia. Individuals with dementia had lower BMI than those without cognitive impairment in late life, and lower BMI has been associated with faster progression of dementia [45]. These latter observations are in accordance with the concept of "frailty syndrome," which has been an independent predictor of dementia (Fig. 1) [46].

The production of inflammatory mediators and hormones by the hypertrophic adipose tissue, vascular dysfunction (including high blood pressure that may impair cerebral perfusion), insulin resistance, and obesity-related gut microbiota changes, which may influence the inflammatory milieu and the gut–brain axis, have been proposed as possible mechanisms that link obesity to increased risk for dementia [36,47]. The role of adipokines, which are cytokines primarily secreted by adipocytes, has gained special attention as these proteins play different roles in the central nervous system (CNS) [45]. Leptin, for example, seems to play a role in learning and memory through action in hippocampal neurons, in addition to being important for the normal development of the hypothalamus [36,45,48]. Of course, this is in addition to its established role in energy homeostasis and food intake, regulating arcuate hypothalamic neurons [36,45]. In contrast, chronic peripheral leptin administration reduced β-amyloid load in an experimental model of Alzheimer's disease and elevated plasma leptin levels were associated with reduced risk for dementia and Alzheimer's disease in humans [49,50]. This has stimulated interest in examining the therapeutic potential of leptin for dementia [45,48].

Neuroimmune pathways underlying the association between obesity and neuropsychiatric disorders

As previously discussed, several behavioral and biological mechanisms have been proposed to justify the association between obesity and neuropsychiatric disorders, but they can vary depending on

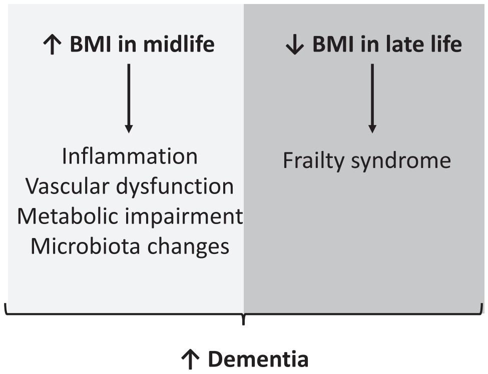

Fig. 1. The association between body mass index (BMI) and risk of dementia. High BMI and central obesity in midlife may increase the risk of dementia later in life. However, after midlife, lower BMI has been associated with frailty and faster progression of dementia.

the specific condition. Figure 2 summarizes the putative biological mechanisms involved in the association between obesity and cognitive and behavioral impairment, highlighting the role played by neuroimmune pathways.

In obesity, adipocyte hypertrophy triggers the recruitment of innate immunity cells and stimulates the production of inflammatory mediators [51]. As a result, a state of low-grade inflammation ensues. The cytokines released by adipocytes reach the circulation and even the CNS, triggering neuroinflammation, especially in the hypothalamus and hippocampus [52]. These brain areas are involved in appetitive behaviors, memory, and learning [52, 53]. An obesogenic diet, such as high-fat diet (especially saturated fat), has been associated with hypothalamic inflammation, which leads to apoptosis of anorexigenic neurons in the arcuate nucleus that compromise the regulation of satiety favoring weight gain [54]. Moreover, peripheral cytokines may influence other CNS processes, such as neurotransmitter metabolism and neuroendocrine activities, leading to mood and behavioral alterations [55]. In humans, the observation of "sickness behavior" in the context of inflammatory diseases and behavioral or depressive changes after treatment with interferon (IFN) are probably the best evidence for that, although the mechanisms are still debated [56]. In the preclinical setting, Dinel et al. showed that an animal model of metabolic syndrome (db/db mice) had increased anxiety-like behaviors and impaired spatial memory performance. In parallel with these mood and cognitive alterations, there were significant increases in the mRNA expression of proinflammatory cytokines (tumor necrosis factor, interleukin [IL]-6 and IL-1β) and decreases in brain-derived neurotrophic factor (BDNF) in the hippocampus of db/db mice [53]. BDNF plays an important role in synaptic plasticity and neuronal survival in the hippocampus and other brain regions implicated in mood regulation and learning [57]. Furthermore, decreases in BDNF brain expression and mutation in the *BDNF* gene have been associated with obesity in human and animal models [58]. Nutritional strategies that prevent weight gain also contribute to normalizing BDNF levels in the hippocampus and to preventing cognitive alterations in mice [59]. In a recent study by Valcarcel-Ares et al., declines in cognitive function were observed in obese and older mice, which was associated with upregulation of genes involved in microglia activation and neuroinflammation in the hippocampus [60].

Inflammation is associated with altered neurotransmitter signaling involved in emotion and cognitive processes (Fig. 3). More specifically, inflammatory cytokines activate the enzymes indoleamine 2,3-dioxygenase (IDO) and GTP-cyclohylase 1, impairing the production of neurotransmitters [52]. The enzyme IDO catabolizes tryptophan into kynurenine, diverting it away from serotonin production. Chronic treatment with IFN-α, used as immunomodulatory therapy in several diseases [61], has been associated with increases in peripheral and central kynurenine levels, along with depressive symptoms [62]. Increases in IDO activity in adipose tissue and decreases in tryptophan plasma levels have been demonstrated in individuals who are obese and have been attributed to obesity-related immune activation [63–65]. Immune activation also increases the activity of the enzyme GTP-cyclohylase 1, which catalyzes the conversion of guanosine-triphosphate (GTP) into dihydrobiopterin, which is then converted into neopterin at the expense of tetrahydrobiopterin (BH4). As BH4 participates in serotonin and dopamine synthesis, increases in neopterin levels theoretically mean reductions in the bioavailability of BH4. Interestingly, increases in neopterin levels have been associated with the number of depressive episodes in major depressive disorder, a condition traditionally associated with reduced levels of serotonin [66]. In this context, it is possible that obesity-related

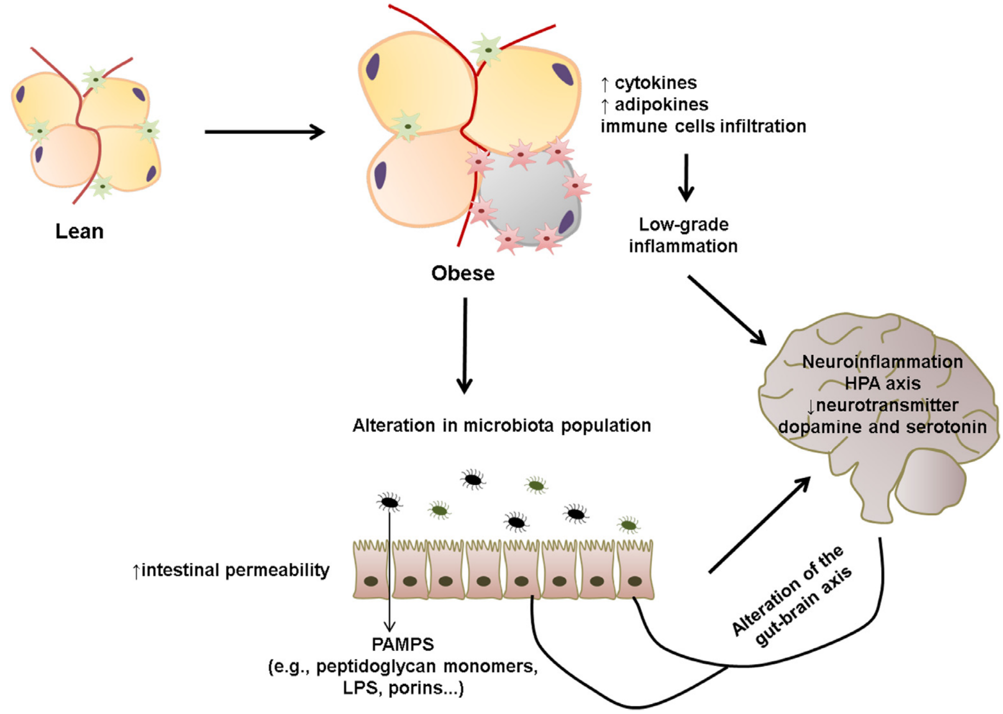

Fig. 2. Putative biological mechanisms involved in the association between obesity and neuropsychiatric disorders. Obesity is characterized by chronic low-grade inflammation, possibly owing to increased secretion of cytokines and adipokines by the adipose tissue where immune cells infiltration can be observed. Obesity is also associated with changes in gut microbiota composition and increased intestinal permeability. Both can lead to activation of an immune response through microbial or pathogen associated molecular patterns (MAMPs or PAMPs, respectively), such as lipopolysaccharide (LPS). The inflammatory molecules can reach the circulation and the central nervous system, where it may cause neuroinflammation. The inflammatory process and immune activation in the brain can affect the hypothalamus–pituitary–adrenal (HPA) axis and neurotransmitter signaling, influencing cognition and behavior.

inflammation contributes to the development or progression of neuropsychiatric symptoms. Conversely, a number of neuropsychiatric conditions, including mood disorders, schizophrenia, and dementia, are also associated with chronic low-grade systemic inflammation and neuroinflammation [56,67–69]. As such, inflammation seems to be a common mechanism that contributes to the pathophysiologic changes in both obesity and neuropsychiatric disorders [70].

Obesity is also accompanied by neuroendocrine changes, in particular involving the HPA axis [71]. A recent meta-analysis by Stalder et al. confirmed the relationship between hair cortisol concentration, a measure of cumulative cortisol levels, with BMI and waist-to-hip ratio [72]. Cortisol, the prototypical stress hormone, plays pivotal roles in pathways that contribute to the development

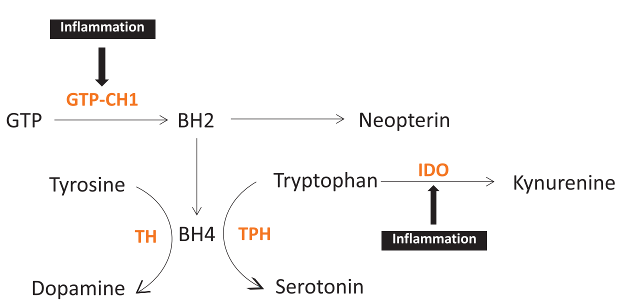

Fig. 3. Inflammation increases the activity of the enzyme guanosine-triphosphate-cyclohylase 1 (GTP-CH1), which catalyzes the conversion of guanosine-triphosphate (GTP) into dihydrobiopterin (BH2). BH2 is converted into neopterin at the expense of tetrahydrobiopterin (BH4) (a cofactor of theenzymes tryptophan hydroxylase [TPH] and tyrosine hydroxylase [TH]). Inflammatory cytokines can also activate the enzyme indoleamine 2,3-dioxygenase (IDO) with catabolizes tryptophan into kynurenine, diverting available tryptophan away from serotonin production.

of obesity, such as appetite, insulin resistance, and redistribution of white adipose tissue to the abdominal region [73]. Activation of the stress system is frequently seen as a trigger or a maintaining factor for mood episodes, psychosis exacerbation, and cognitive decline [70,74,75]. Again, both obesity and neuropsychiatric conditions may share a similar pattern of HPA axis activation.

Growing evidence suggests the role of gut microbiota in brain functioning through the regulation of inflammatory response and HPA axis [76]. Some factors such as diet, drugs, comorbid diseases, and genetic factors have been implicated in changes of gut microbiota composition, and, as consequence, in the development of metabolic and neuropsychiatric disorders [77]. Alteration in the prevalence of symbiotic versus pathogenic bacteria in the gut leads to the activation of immune cells residing in the intestinal mucosa. This, in turn, may influence the gut–brain axis, herein defined as a complex bidirectional interaction between the gut and the brain with the participation of the enteric nervous system and the vagus nerve [76,78–83]. Disruption in the gut bacterial composition has already been implicated in obesity as well as in several neuropsychiatric disorders [76,78–83].

Changes in gut bacteria populations caused by obesity and unhealthy behaviors, including diet, are associated with gut permeability to macromolecules [84]. Interestingly, patients with depression also display increases in gut bacterial translocation and activation of immune responses [85,86]. Bacteria have a peptidoglycan cell wall that may activate the immune system, leading to inflammatory response. Microbial -associated molecular patterns, such as lipopolysaccharide and porins, are peptidoglycan of gram-negative bacteria cells, which may cause activation of immune cells, partly explaining obesity-related inflammation [87,88]. The systemic inflammation observed in obesity may contribute to the development of neuroinflammation and to the activation of the aforementioned pathways, affecting neurotransmitter production, HPA axis function, and ultimately, cognition and behavior [78,89].

The relationship between the gut and the brain becomes more evident when manipulation in gut microbiota through probiotics influences mood and cognition. In a preclinical study, the use of the probiotic bacterium *Bifidobacterium infantis* promoted reduction in inflammatory response and increased plasma concentration of tryptophan, improving depressive-like symptoms in mice [90]. The pivotal clinical trial by Messaoudi et al. with healthy volunteers who received *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 or a placebo for 30 d showed decrease in depressive symptoms in the group taking probiotics [91]. A recent systematic review and meta-analysis of randomized controlled trials support the concept that the use of probiotics may be associated with a reduction of depressive symptoms [92]. The use of probiotics has been associated with positive effects in cognitive measures in patients with Alzheimer's disease [93]. Previous randomized placebo-controlled trials also suggest the potential role of probiotic interventions in schizophrenia [94–96]. Further investigation into the role of probiotics in neuropsychiatric disorders, including the role of specific bacteria strains, is warranted.

Conclusion

Obesity has been associated with cognitive and behavioral syndromes. The understanding of the mechanisms underlying this association is still in its infancy and may involve exacerbation in inflammatory pathways that may cause neuroinflammation, and changes in the HPA and gut–brain axis.

Owing to the intricate relationship between obesity and neuropsychiatric disorders, addressing one of these conditions may affect the other. A better understanding of the pathways involved in the link between obesity and neuropsychiatric disorders can contribute to development of therapeutic strategies for these conditions.

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