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Feature Review

The menace of obesity to depression and anxiety prevalence

Stephanie Fulton,[1,*] Léa Décarie-Spain,[2] Xavier Fioramonti,[3] Bruno Guiard,[4] and Shingo Nakajima[1]

The incidence of depression and anxiety is amplified by obesity. Mounting evidence reveals that the psychiatric consequences of obesity stem from poor diet, inactivity, and visceral adipose accumulation. Resulting metabolic and vascular dysfunction, including inflammation, insulin and leptin resistance, and hypertension, have emerged as key risks to depression and anxiety development. Recent research advancements are exposing the important contribution of these different corollaries of obesity and their impact on neuroimmune status and the neural circuits controlling mood and emotional states. Along these lines, this review connects the clinical manifestations of depression and anxiety in obesity to our current understanding of the origins and biology of immunometabolic threats to central nervous system function and behavior.

Highlights

Obesity increases the incidence of depression and anxiety as a function of the extent of metabolic dysfunction.

Diets that include excess saturated fat and sugar intake promote metabolic dysfunction, neuroinflammation, and mental health impairments.

Adipose- and gut-derived inflammation and changes in brain nutrient composition stimulate neuroinflammation.

Neuroinflammation alters structure, excitability, and connectivity in corticolimbic networks controlling mood, motivation, and emotion.

Convergence of mood and metabolic deficits

The peril of mood and anxiety disorders is receiving increasing attention beyond psychiatric and psychological research and practice, an expansion encouraging constructive awareness and discussion in public forums. The centrality of mental health to overall wellbeing and the substantial contribution of external stressors has never been more apparent. The major influence of internal, biological stressors originating from alterations in energy metabolism has also earned significant consideration. In keeping with its extensive impact on physiology and health, growing evidence is accentuating the threat of obesity to central nervous system function and risk of psychiatric illness. Depression and anxiety disorders are prevalent and disabling mental health conditions and the increased hazard they pose for obese individuals is far-reaching. Beyond hindering personal welfare and quality of life, depressed mood and anxiety can diminish the will to seek out and adhere to therapeutic interventions. The interchange between metabolic and mood dysfunction can perpetuate a cycle of despair, overeating and physical inactivity that enhances obesity severity and numerous associated health risks. In view of these consequences and the limitations of available therapies, it is critical to improve our knowledge of the dietary, metabolic, and neurobiological effectors of depression and anxiety development and progression to implement better preventative and treatment strategies.

An elevated body mass index (BMI) is predictive of a chronic course of depressive and anxiety symptoms [1,2]. The odds of developing major depressive disorder (MDD) and anxiety increase as a function of the number of coexisting metabolic impairments, such as those characteristic of metabolic syndrome [3,4]. Obesity is coupled to various structural and functional changes in the brain that are remarkably similar to those observed in depressive disorders, such as region-specific increases in cell density and compromised neural connectivity and excitability [5,6]. Several lines of evidence suggest that prolonged inflammation caused by poor dietary lifestyle and inactivity and resulting metabolic consequences are required for such outcomes. Clinical observations combined with rodent models of obesity exhibiting depressive- and anxiety-like behaviors are proving valuable for uncovering the immunometabolic and neural mechanisms

[1]Centre de Recherche du Centre Hospitalier de l'Université de Montréal (CRCHUM), Department of Nutrition, Université de Montréal, Montréal, QC H3T1J4, Canada
[2]Centre de Recherche du Centre Hospitalier de l'Université de Montréal (CRCHUM), Department of Neuroscience, Université de Montréal, Montréal, QC H3T1J4, Canada
[3]NutriNeuro, UMR 1286 INRAE, Bordeaux INP, Bordeaux University, Bordeaux, France
[4]Centre de Recherches sur la Cognition Animale (CRCA), Centre de Biologie Intégrative (CBI), CNRS UMR5169, UPS, Université de Toulouse, Toulouse, France

*Correspondence:
stephanie.fulton@umontreal.ca
(S. Fulton).

involved. In this review, we focus on how obesity increases the risk for depression and anxiety (for cognitive corollaries, see [7,8]), with the aim to illuminate the diverse metabolic culprits of obesity and their influence on the neural and behavioral processes giving rise to mood and emotional deficits.

Epidemiology and clinical features

MDD (or depression) is a debilitating condition with genetic, epigenetic, and environmental contributions. Depression can manifest in various ways, modulating homeostatic functions such as appetite and sleep that can in turn further alter mood. Anxiety accompanies depression in most cases and is indicative of a poorer mental health prognosis. Melancholic depression, the most common form, is distinguished by hypophagia, hyposomnia, and anhedonia (decreased capacity to experience and anticipate pleasure). In addition to anhedonia, characteristics of the atypical subtype of depression include hyperphagia, lethargy, and hypersomnia. Obese individuals, particularly those presenting attributes of metabolic syndrome (abdominal obesity, hyperglycemia, hypertension, elevated triglycerides), tend to develop the atypical subtype [9] (Box 1). This form of depression has stronger links to peripheral [10,11] and central [12] inflammation. Individuals with atypical depression often have a more unrelenting course of depression [13], in part because they show a poorer response to antidepressants [14]. As atypical depression is predictive of overeating and weight gain, and metabolic risks can be intensified by antidepressant treatments that encourage weight gain, a vicious cycle can promote disease progression.

The link between obesity and depression is well established. There is a bidirectional association between being overweight (BMI ≥ 25–29.99) and depression in men and women, a relationship that is stronger for obesity (BMI ≥ 30) [15]. A meta-analytic overview illustrates that obese adults self-reporting symptoms have 23–36% increased odds of developing depressed mood as compared with nonobese controls, whereas clinically diagnosed MDD is elevated by 14–34% [2]. The odds of depression are higher when evaluating the waist-to-hip ratio [16,17] which provides a better estimate of visceral adiposity and metabolic dysfunction than BMI [18]. Emphasizing the importance of early detection and treatment, a longitudinal meta-analysis suggests that obese adolescents have a 40% increased risk of being depressed [19]. A similar positive relationship is observed with anxiety: obesity heightens the odds of an anxiety disorder or anxiety symptoms (e.g., dread, unease) by 30% and 40%, respectively [1,20]. As with depression, other variables may moderate the association between obesity and anxiety, including the degree of obesity, presence of cardiometabolic comorbidities, and the type of anxiety. Indeed, there is a stronger relationship between severe obesity (BMI ≥ 35) and anxiety [1].

Box 1. Sex, gender, and metabolic risks

The frequency of depression and anxiety disorder diagnoses are approximately double for obese women as compared with obese men [1,157], a divergence that corresponds with lifetime prevalence independent of body weight. This sex distinction in incidence narrows considerably in conditions of severe obesity (BMI ≥ 40) [1]. While sex differences in anxiety disorders and major depression are well characterized, its only more recently that dissimilar underlying mechanisms are emerging (for review, see [158]). Adiposity serves as a better predictor of depression than body weight in women than in men [149]. Women with depression and anxiety are more likely to have increased appetite and weight gain than male counterparts [150], an outcome associated with the effects of stress to stimulate palatable food intake [119]. In both sexes, negative mood state is more robustly associated with metabolic impairments such as inflammation, hypertension, and insulin resistance rather than body weight itself [3]. Correspondingly, the prevalence of MDD is nearly twice as high in people with type 2 diabetes [159] and more than threefold higher in people with type 1 diabetes than those without, with greater rates in diabetic women than men [160]. Diabetes is associated with a 48% greater likelihood of anxiety symptoms and a 20% higher risk of developing an anxiety disorder [20]. In a consistent manner, obese individuals characterized as metabolically healthy (normal blood pressure, C-reactive protein, triglycerides, and glycaemia) present either no increased risk [161] or a modest elevated risk [3] of depression diagnosis as compared with nonobese controls. However, obesity stigmatization and poor self-image may still contribute to negative mood states for these individuals, a problem more evident in women.

Food environment and nutrient actions

Contemporary dietary environments offer an abundance of processed foods that are very tasty and abnormally energy-dense, in addition to foods that convey gustatory information associated with learned caloric value but then fall short post-ingestion (e.g., noncaloric sweeteners). Sensory cues remind us of their affective value and bombard us with information about their proximity and the comparatively low effort and cost required to obtain. These relatively recent changes to our external world perilously intersect with the neurobiological processes controlling feeding, which include critical components that favor positive emotion and stress reduction and facilitate the encoding of memories related to how to access these foods and how they make us feel in different contexts. Residing in midbrain and corticolimbic neural circuits, these processes are highly recruited by our modern food environment and are posited to be largely responsible for high rates of obesity and associated disease.

Dietary fat overload

Several lines of evidence link poor diet, inflammation, and depressive symptomology [21,22]. Dietary fats can have different metabolic, endocrine, and behavioral effects according to their lipid class. Prolonged saturated fat intake can interfere with energy homeostasis by stimulating visceral adipose deposition and inflammation in humans [23] and impairing central leptin and insulin signaling in rodents [24,25]. Consumption of saturated fats [26] and plasma concentrations of the saturated fatty acid palmitate [27] positively correlate with depressive symptoms and plasma levels of the acute phase reactant C-reactive protein (CRP) in humans. The causal relationship of diet-induced obesity (DIO) to depression and anxiety development in human studies is indirect. To this end, rodent research has revealed that prolonged high-fat diet (HFD) elicits metabolic dysfunction and increases anxiety- and depressive-like behaviors [28–36], heightens stress and hypothalamic–pituitary–adrenal (HPA) responses [37,38], and triggers neurobehavioral deficits associated with blunted mesolimbic dopamine function [39–41]. These outcomes appear to largely stem from the immune-stimulating properties of excess fat intake that propagate metabolic and vascular disturbances and enhance neuroinflammation.

Numerous epidemiological findings point to metabolic and affective benefits of a Mediterranean-like diet, rich in unsaturated fats. Oleate, a monounsaturated fatty acid enriched in olive oil, can improve glycemic control and plasma lipid profiles in humans and protect against inflammation, hyperphagia, and anxiodepressive behaviors in mice [34,42]. Omega-3 (n-3) polyunsaturated fatty acids (PUFA), including docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), are well-known for their anti-inflammatory actions. Increased dietary n-3 intake can improve insulin sensitivity [43] and significantly diminish plasma CRP, interleukin-6 (IL-6), and tumor necrosis factor alpha (TNFα) levels in humans [44]. Several reports link higher n-3 consumption with lower prevalence and severity of mood disturbances in humans [45] and demonstrate that n-3 supplementation dampens neuroinflammation and attenuates behavioral indices of mood deficits in rodents [46,47]. In contrast, low levels of blood n-3 PUFA correlate with heightened inflammatory status and depression risk in humans, whereas imposed dietary n-3 deficiency in rodents diminishes brain n-3 levels and stimulates neuroinflammation and anxiety- and depressive-like behaviors [47].

In addition to being utilized by and stored in neural cells, lipids are fundamental structural components that affect membrane fluidity, signaling, and neuroplasticity. Brain transport of fatty acids is elevated in individuals with metabolic syndrome [48]. Moreover, chronic saturated high-fat feeding increases saturated fatty acid levels and appreciably decreases PUFA levels in the brain of rodents [49], changes that are likely one means by which saturated dietary fats generate neuroinflammatory responses and mood deficits. The type and amount of dietary fat can affect membrane phospholipid PUFA composition and associated metabolites (peroxidation products;

specialized proresolving mediators) that contribute to neuroimmune activity and neural function. Moreover, PUFAs are precursors for endocannabinoids, with known effects on immunomodulation, neuroinflammation, food intake, and mood. Indeed, membrane n-3 composition is blunted in individuals with mood disorders, a finding that gave rise to the phospholipid PUFA hypothesis of depression [50]. Both EPA and DHA limit the inflammatory effect of eicosanoids derived from arachidonic acid, an omega-6 fatty acid with plasma levels that positively correlate with MDD severity and reduced serotonin transporter binding in the brain [50]. In parallel, fatty acids can modulate intracellular signaling cascades: EPA and DHA both act as competitive antagonists of the Toll-like receptor-4 (TLR4) signaling pathway [47], which mediates the proinflammatory activity of lipopolysaccharides (LPS) and saturated fatty acids like palmitate. N-3 PUFA can also inhibit nuclear factor kappa-B (NFκB) activity, including through receptors like GPR120 in mice. Correspondingly, central GPR120 agonism can suppress anxiety-like behaviors in mice exposed to a saturated HFD [51]. The collective central actions of saturated dietary fats to decrease PUFA phospholipid-derived metabolites and increase proinflammatory signaling looms large as a culprit in the development of depression and anxiety in obese individuals.

Consequences of excess sugar

Ample evidence directly connects obesogenic diets to depressive- and anxiety-like behaviors in rodents; however, the contribution of excess sugars typically present in such diets demands attention. While sugar consumption can alleviate stress and pain and improve negative mood and emotional states in the short-term [52], prolonged intake of high sucrose or fructose diets can induce anxiety- and depressive-like behaviors and motivational deficits [53–55], effects that are more pronounced during the adolescent period [55–57]. The presence of excess sugar in a HFD was shown to be necessary for hypothalamic inflammatory responses in mice, including the activation of microglia, the resident immune cells of the brain [58]. Combined high-sugar and -fat consumption induces glucolipotoxicity in pancreatic beta cells, a phenomenon impairing insulin secretion and worsening metabolic health. The extent to which combined sugar and fat surfeit have similar direct actions in neural networks, controlling mood and emotion, remains to be determined. Brain glucose transport and metabolism can be both increased or decreased by obesity, depending upon the structure under investigation [59]. Reductions in glucose uptake in the hippocampus have been connected to cognitive deficits in obesity [59]. It is well known that glucose can also alter the electrical activity of specialized neuronal populations in the hypothalamus [60]; whether these glucose-sensing neurons are involved in the control of mood remains to be elucidated. The fructose transporter GLUT5 is expressed in glia; thus, the possibility that excess intake of foods high in fructose directly triggers neuroimmune responses that underlie depression warrants investigation. It is nonetheless clear from the collection of studies examining the influence of diet and nutrients, that the nature and amount of dietary fat and sugars consumed can have a potent influence on metabolic and mental health.

Inflammatory conduits to the brain

Peripheral immune activation figures prominently in the pathophysiology of psychiatric and metabolic disorders and resonates as a prime instigator of depression onset in obesity. Depression in a subgroup of individuals is associated with elevated circulating levels of proinflammatory cytokines, chemokines, and cell adhesion molecules, as well as prostaglandins and other arachidonic acid derivatives [61]. Inflammation-induced depressed mood can be predicted by elevated blood mononuclear cell transcription factor activity related to immune activation (NFκB), sympathetic activation, and glucocorticoid (GC) insensitivity [62]. Likewise, individuals suffering from anxiety disorders can exhibit elevated circulating levels of inflammatory markers, including CRP, IL-1β, IL-6, and TNFα [63]; however, the literature linking inflammation to anxiety is much sparser. Additional evidence contributing to neuroimmune theories of depression and anxiety arise from

observations that inflammatory interventions can lead to symptoms of these disorders, such as in the case of patients receiving interferon (IFN) alpha treatment [64]. Obesity is often characterized by low-grade inflammation that contributes to the development of metabolic and vascular impairments. Obese individuals exhibiting elevated inflammation, particularly increases in CRP, are more likely to meet criteria for metabolic syndrome and to develop MDD and anxiety [65]. CRP is a protein secreted by the liver in response to an increase in circulating proinflammatory cytokines, most notably IL-6 and to a lesser degree IL-1β and TNFα. Notably, large cohort studies report higher CRP concentrations in depressed patients, making heightened CRP levels in obesity one of the best predictors of depression onset, particularly atypical depression [66]. Dietary-derived saturated fatty acids [26] and erythrocyte content of saturated fatty acids (indicator of long-term consumption) [27], positively correlate with circulating measures of CRP and can contribute to inflammation by favoring TLR4 signaling in macrophages [67]. In turn, both diet and serum indices of inflammation associate with indices of emotional distress. In this section, we explore the major tissue origins of inflammation in obesity and summarize their involvement in mood and emotional deficits (Figure 1).

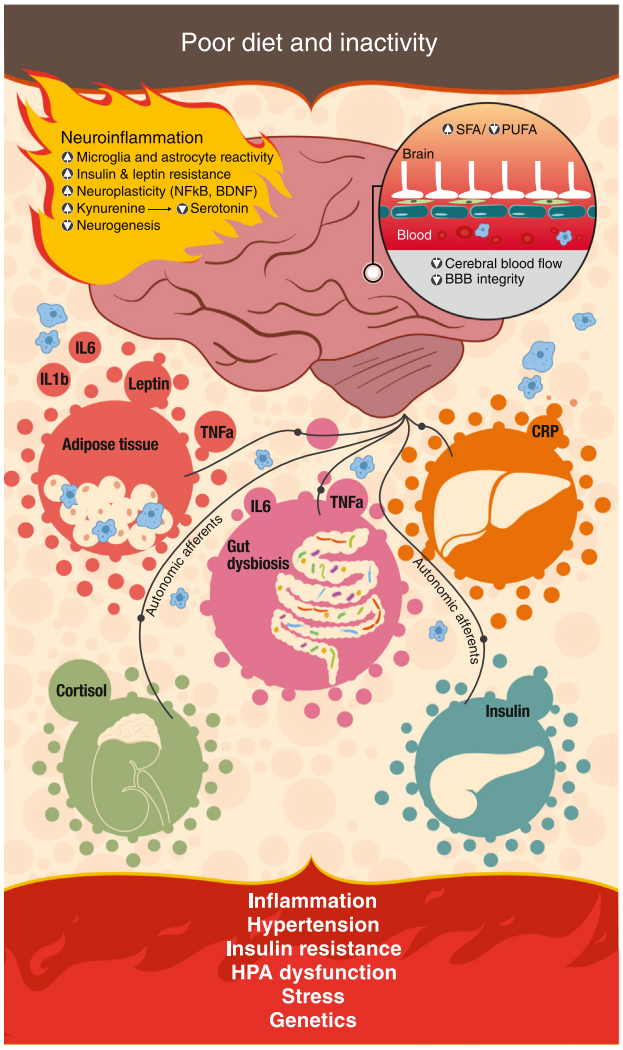

Figure 1. Peripheral and neural alterations linked to depression and anxiety risk in obesity. Lifestyle habits that include overconsumption of fats and sugar and sedentation drive obesity development and metabolic dysfunction. Excessive adipose accumulation in visceral depots caused by poor diet (along with chronic stress and genetics) is especially susceptible to immune cell infiltration and cytokine secretion. Aided by alterations in gut microbiota that promote dysbiosis, a chronic inflammatory state develops that favors and/or associates with metabolic risks (e.g., insulin resistance, hypertension) and contributes to neurovascular impairments (including weakened BBB integrity), neuroinflammation, and neuroplasticity in mood networks. Elevations in circulating CRP serve as a useful inflammatory index and predictor of depression onset. The neurovascular unit (insert) includes endothelial cells that control interactions with different vascular, immune, and neural cells. Changes in brain composition and handling of lipid species (saturated versus unsaturated) and sugars (glucose/fructose) associated with DIO are also implicated in neuroimmune activation and changes in brain structure, connectivity, and excitability. Abbreviations: BBB, blood–brain barrier; BDNF, brain-derived neurotrophic factor; CRP, C-reactive protein; DIO, diet-induced obesity; HPA, hypothalamic–pituitary–adrenal; NF B, nuclear factor kappa-light-chain-enhancer of activated B cells; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid. Illustration created by Charlie Padgett.

Adipose expansion

The production of proinflammatory cytokines by white adipose tissue is a major source of obesity-related inflammation. Excess fat and sugar consumption favor the accumulation of visceral adipose tissue, which comprises a higher concentration of saturated fatty acids and is especially vulnerable to immune insults as compared with subcutaneous fat [18]. Correspondingly, depression incidence is higher when assessing abdominal adiposity or the waist-to-hip ratio as compared with BMI [17]. The importance of excessive adipose mass to emotional deficits in obesity is highlighted by rodent studies showing that prolonged saturated high-fat feeding that does not lead to significant adipose deposition fails to stimulate anxiety-like behaviors [37,38]. However, in the absence of obesity development, these diets can still potentiate HPA reactivity [37] and feedback [38] and suppress behavioral responses to rewards [41]. When under metabolic stress, adipocytes produce inflammatory mediators and chemoattractant molecules, such as monocyte-chemoattractant protein-1 (MCP1), that can both activate resident immune cells and recruit bone marrow-derived immune cells. It is namely resident macrophages and T-lymphocyte immune cells that perpetuate the inflammatory situation in adipose tissue [68], and dietary saturated fatty acids can be a direct source of metabolic stress that can promote inflammation by increasing TLR4 signaling. Adipose-derived inflammatory molecules such as TNFα disrupt insulin signaling to promote resistance and impaired vascular health. As these immunometabolic consequences heighten the risk of depression [3], abdominal adipose expansion plays a central role in the transmission of peripheral inflammation to the CNS.

Gut dysbiosis

Gut flora contribute to energy balance by influencing nutrient absorption and controlling fiber fermentation. Microbiota are also the main source of endotoxins (LPS), which are well-known contributors to systemic inflammation. Several bacteria can produce other metabolites that can impact physiology and health, such as short-chain fatty acids, and several molecules with that can affect neural signaling and excitability in mood networks, including serotonin and gamma-aminobutyric acid (GABA) [69]. Diet is the primary effector of microbiota composition, but psychological stress can also modulate flora in rodents and in patients with MDD [69,70]. In addition, mounting evidence suggests that microbiota alterations mediate diet-induced parental programming of offspring neurobehavioral function and mood disorder susceptibility [71]. Chronic changes in microbiota composition in obesity (dysbiosis) are associated with inflammation, insulin resistance, and mental health deficits [72]. Notably, both the obese phenotype [73] and anxiodepressive behaviors [74] are transmissible by transplanting gut microbiota of DIO to normal-weight, germ-free mice. Moreover, the microbiota from DIO mice can weaken endothelial tight junctions and trigger inflammation in both intestine and brain and promote brain insulin resistance [73,74]. Saturated high-fat feeding and obesity can induce phylum-wide shifting in microbiota, from Bacteroidetes to Firmicutes [73], and the abundance of some Firmicutes species positively correlate with energy intake and plasma CRP levels in obese children. Deletion of T cell-dependent immunoglobulin A production enhances obesity, while reducing the abundance and diversity of *Clostridium* [75]. Interestingly, significant reduction of *Clostridium* is also observed in MDD patients and its abundance is negatively correlated to the severity of anxiety and depression [70]. While changes in microbiota composition are reported in individuals with MDD and can correlate with disease severity, the nature of microbiota alterations across studies are conflicting [76]. The mechanisms by which gut microbiota regulate brain function remain unclear; however, the inflammatory consequences of dysbiosis are well-positioned to contribute to psychiatric and neurological comorbidities of obesity.

Neuroimmune components

Peripheral immune activation can exert profound effects on the brain and behavior. While neuroinflammation in the absence of peripheral inflammation can occur, behavioral is more affected by

systemic immune responses that extend to the CNS. Acute neuroimmune activation can bring about physiological and behavioral changes that are adaptive to the organism, such as fever, HPA activation, and psychomotor slowing. However, persistent peripheral inflammation, even if low-grade, can elicit sustained neuroinflammatory actions that ultimately generate changes in brain structure, connectivity, and excitability [61]. Microglia and astrocytes are the brain-resident glial cells undertaking immune functions in pathological states. Under robust inflammatory conditions, blood-borne myeloid cells can infiltrate the brain to generate neuroimmune responses at the interface between the parenchyma and the circulation. These include macrophages that can interact with endothelial cells of the BBB and the neurovascular unit (Box 2). Together, activated glia and centrally recruited myeloid cells determine the extent of neuroinflammatory responses by production of local cytokines and chemokines and the stimulation of intracellular signals such as NFκB, JNK, and JAK-STATs (Figure 2). Microglia dominate as contributors to neuroinflammation and several reports underscore their role in the neuroimmune pathogenesis of depression [77]. In addition, monocytes can infiltrate the brain and differentiate into microglia that produce an inflammatory response that contributes to anxiety-like behavior [78]. Human neuroimaging findings show heightened microglia activation after LPS administration that produces depressive-like sickness symptoms [79]. Consistently, suppression of microglia [80] and astrocyte [81] reactivity is implicated in the response to antidepressant therapies.

There are numerous ways that peripheral inflammation can affect brain immune function: (i) some cytokines, like TNFα, IL-6, and IL-1β can cross the blood–brain barrier (BBB) through leaky regions (exacerbated by metabolic and vascular dysfunction) or via saturable transport to act directly on glia and neurons; (ii) circulating cytokines and chemokines can target receptors on astrocytes and endothelial cells that form the BBB and activate perivascular macrophages to produce local inflammatory cytokines, chemokines, prostaglandins, and nitric oxide; (iii) monocytes, macrophages, and T cells can traffic to the brain to secrete cytokines; and (iv) activation of peripheral autonomic afferents that relay cytokine signaling to the brain.

Intersecting neural circuits controlling mood and body weight

Emotions and mood states are controlled by neural processes residing in midbrain, limbic, and cortical sites (Figure 2) that are often referred to as components of brain reward circuitry due to their contribution to encoding reward value associated with stimuli (e.g., food) and behavioral actions (e.g., feeding). A pivotal feature of these circuits is their modulation in response to experiences, which largely serves to orient future behavior towards or away from objects or actions. Dopamine neurons of the ventral tegmental area that project to the nucleus accumbens have been intensely studied and implicated in the control of motivated behavior (including food-motivated behavior), adaptation to behavioral outcomes, and anhedonia, a core symptom of

Box 2. Vascular pathology and blood–brain barrier (BBB) integrity

The BBB protects the CNS from toxins and pathogens and alterations of these properties are a component of some neurological and psychiatric diseases. The walls of the blood vessels comprise endothelial cells that control interactions with different vascular, immune, and neural cells. Astrocytes, pericytes, and the extracellular matrix contribute to the formation of this neurovascular unit (see Figure 1 in main text, zoom inset). Patients with chronic vascular conditions, including diabetes, cardiovascular disease, and stroke, have an increased risk of developing depression. Obesity and cardiometabolic comorbidities impair BBB integrity [162]; thus, increased brain penetrability stands as a mechanism favoring neuroimmune activation, immune cell infiltration, and mood dysfunction. The breakdown of the BBB produced by peripheral immune challenge (LPS) permits passage of bone marrow-derived immune cells into the brain, a process enhanced by DIO [163] and that favors depressive behaviors [164,165]. Hypertension is a leading risk factor for depression incidence in obesity and causes neurovascular changes that involve the actions of perivascular macrophages to stimulate oxidative stress and inflammation that lead to cognitive dysfunction [166]. Interestingly, chronic stress itself can also lead to BBB dysfunction in the nucleus accumbens to promote depressive-like behaviors in mice, changes linked to increased monocyte accumulation and reduced neuronal cAMP production [167].

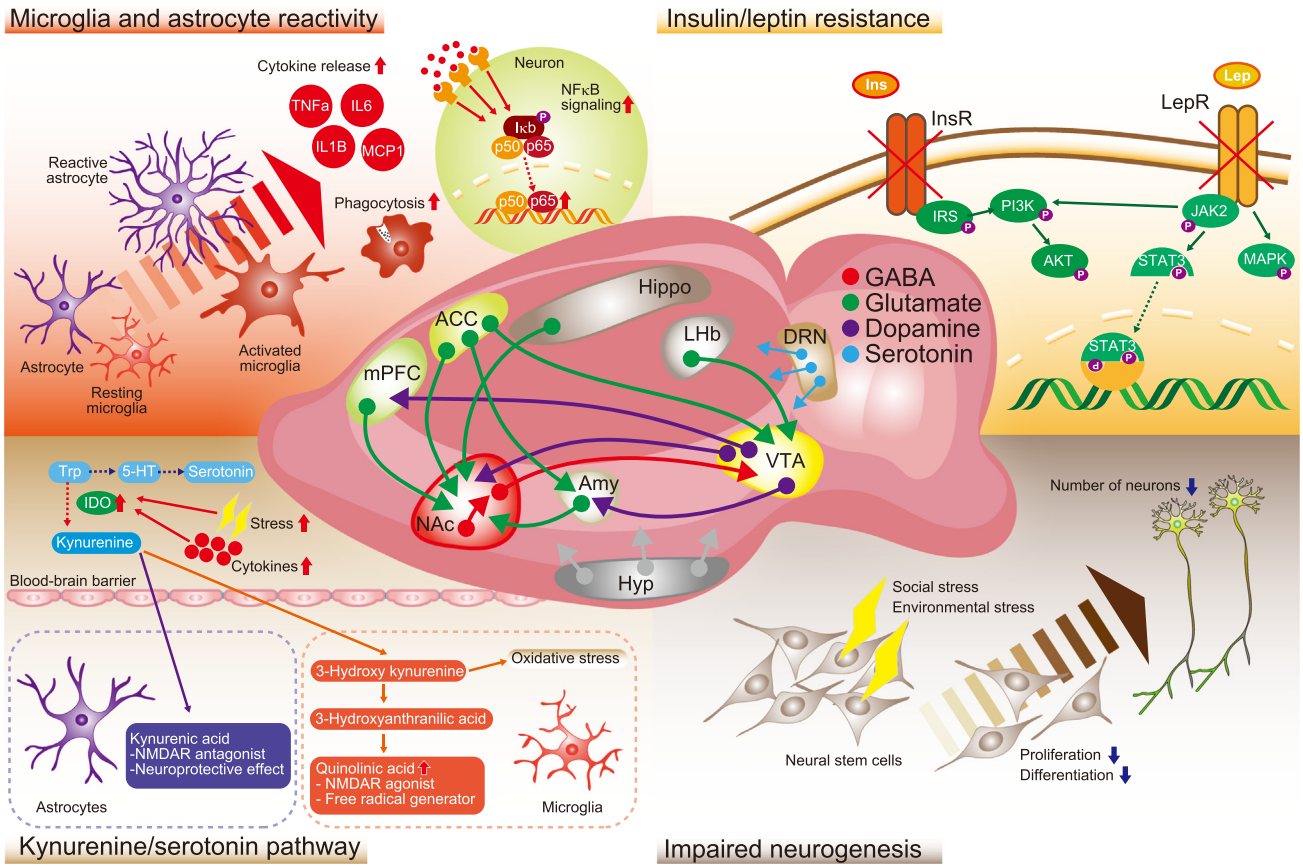

Figure 2. Central regions and mechanisms implicated in obesity-induced depression and anxiety. Schematic of rodent brain with key nuclei and pathways, surrounded by mechanisms proposed to contribute towards the manifestation of depressed mood and anxiety symptomology in conditions of obesity. Center: principal nuclei and circuits. The DRN is the largest of the serotonergic nuclei and sends highly divergent projections that target many functionally distinct regions controlling motivation, arousal, sleep, mood, and autonomic functions. Dopamine neurons of the midbrain VTA form the mesolimbic dopamine system and are highly implicated in reward learning, motivation, and anhedonia features of depression. The corticolimbic nuclei receiving dopaminergic and/or serotoninergic inputs are highly interconnected. The nucleus accumbens is considered as a hub strongly contributing to motivation that receives dense glutamatergic innervation from multiple sites, thereby integrating signals encoding learning, memory, emotion, and evaluation and translating this into behavioral action via basal ganglia outputs. Peripheral panels: evidence amassed to date implicates four general, overlapping cellular mechanisms in the pathophysiology of depressed mood and anxiety stemming from obesity: (i) microglia and astrocyte reactivity, neuroinflammation, and resulting neuroplastic changes (e.g., changes in brain-derived neurotrophic factor expression); (ii) insulin and leptin resistance in neural cells; (iii) kynurenine/serotonin pathway and changes in glial function; and (iv) deficits in hippocampal neurogenesis. Each of these mechanisms has been tied to local neuroinflammatory responses and/or the immunometabolic consequences of poor diet and obesity. Abbreviations: ACC, anterior cingulate cortex; Amy, amygdala; DRN, dorsal raphe nucleus; GABA, gamma-aminobutyric acid; Hippo, hippocampus; 5-HT, 5-hydroxy tryptophan; Hyp, hypothalamus; IDO, indoleamine-2,3-dioxygenase; IL, interleukin; Ins, insulin; InsR, insulin receptor; IRS, insulin receptor substrate; JAK2, Janus kinase 2; Lep, leptin; LepR, leptin receptor; MAPK, mitogen-activated protein kinase; MCP1, monocyte-chemoattractant protein-1; mPFC, medial prefrontal cortex; NAc, nucleus accumbens; NMDAR, *N*-methyl-D-aspartate (glutamate) receptor; PI3K, phosphoinositide 3-kinase; SN, substantia nigra; STAT3, signal transducer and activation of transcription 3; TNFa, tumor necrosis factor alpha; Trp, tryptophan; VTA, ventral tegmental area.

depression. Dopamine neurons also innervate the prefrontal cortex and amygdala, among other areas, and each of these regions is interconnected. The nucleus accumbens receives dense glutamatergic innervation from the prefrontal cortex, amygdala, and hippocampus and these areas reciprocally connect with one another and receive serotonergic inputs from the dorsal raphe nucleus, in addition to inputs from hypothalamic nuclei controlling homeostatic, endocrine, and autonomic functions. The nucleus accumbens has been heavily implicated in food-directed behavior and is tied to the hedonic and motivational deficits associated with depression, while

the hippocampus has been underscored in cognitive impairments. The amygdala controls fear responses and is implicated in feelings of dread and apprehension that are central to anxiety. Other highly pertinent regions include the lateral habenula and the anterior cingulate cortex. Neuronal activity in the lateral habenula is associated with encoding value of cues previously paired with aversive outcomes and is posited to contribute to anhedonia [82]. The anterior cingulate cortex is deemed to be involved in behavioral flexibility, conflict monitoring, and reward-based decision making, and neuroinflammation in the anterior cingulate cortex is tied to clinical features of atypical depression [12]. As targets of deep-brain stimulation therapy, both nucleus accumbens and ventral anterior cingulate cortex stimulation are associated with strong antidepressant effects in treatment-resistant MDD patients [83].

Neuroinflammatory outcomes

Neuroimaging studies demonstrate structural alterations in obesity, most consistently decreases in cortical grey matter that are strikingly comparable with those observed in individuals with mood disorders [6]. Both waist circumference [84] and circulating markers of inflammation [85] in obesity correlate negatively with cortical grey matter volume. Of significance, mounting reports demonstrate obese individuals possess greater subcortical volumes in areas controlling reward and emotion. Novel diffusion spectrum neuroimaging techniques reveal increased subcortical cell density in obesity, observations associated with activated microglia and astrogliosis in neuroinflammatory conditions. Obese adults exhibit increased cellularity in the hippocampus and amygdala [86], whereas greater cell density in the nucleus accumbens, dorsal striatum, pallidum, hypothalamus, amygdala, and hippocampus correlates positively with waist circumference in adolescents [5]. Radiologic evidence of brain gliosis that links to insulin resistance in obese adults has also been reported [87]. Accentuating a role for immunometabolic processes, elevated plasma cytokines and insulin resistance have been tied to structural and functional changes in reward- and motor-relevant cortical and subcortical structures controlling mood. For example, anhedonia and motor slowing are associated with increased plasma CRP and insulin resistance that correlate negatively with functional connectivity in corticolimbic reward and motor circuits [88]. Together, these findings expose glial reactivity along with structural and functional changes in mood networks that associate with adiposity and inflammation in humans.

Corroborating and extending findings in humans, rodent investigations illustrate the impact of high-fat and -sugar diet to stimulate reactive gliosis and upregulate cytokine and chemokine gene expression in mouse hypothalamus [89], hippocampus [90,91], nucleus accumbens [34], and ventral tegmental area [92]. Microglia and astrocytes are paramount for the inflammatory pattern induced by saturated high-fat feeding and consequent metabolic impairments [93,94]. A revealing aspect of hypothalamic inflammatory markers is that they are evident as early as 3 days of high-fat feeding, prior to significant adipose expansion and peripheral inflammation, suggesting that caloric overload may participate towards adaptive inflammatory signal upregulation via direct nutrient–brain and/or endocrine actions [95]. This early immune response to high-fat feeding in mice resolves temporarily, to re-emerge more potently and in a manner coupled to weight gain and metabolic dysfunction, with signs of neural degeneration observed by 8 months [95]. Reversing neuroinflammation via targeted genetic [96,97], pharmacological [98,99], or dietary [49,100] approaches that rescue behavioral anomalies offers convincing support for a causal role of neuroinflammation in obesity-induced neuropathophysiology. For example, anxiodepressive behaviors elicited by chronic saturated HFD can be reversed via selective inhibition of NFκB activation in the nucleus accumbens, in a manner that corresponds with an alleviation of nucleus accumbens inflammatory status [34]. Reducing nucleus accumbens NFκB-mediated inflammation also blocked compulsive sucrose-seeking in these obese mice, a finding that bodes well with evidence that overeating, a feature of atypical depression, is

associated with immunometabolic dysfunction. The collective findings in rodents, along with reports of structural and functional changes in obese humans, support the clinical relevance of this mechanism.

Neuroplastic adaptations

The flexibility of neural circuits controlling mood and emotion is governed by neuroplasticity mechanisms that permit changes in connectivity and synaptic strength in response to internal (e.g., metabolic) and external (e.g., stress) states. Cytokines play an essential role herein under physiological conditions, including in neurogenesis and synaptic plasticity. However, sustained elevations in cytokines and chemokines by HFD can elicit region-specific, nonhomeostatic alterations in neuroplasticity to promote mood deficits and weight gain. Indeed, recent methylome-wide studies implicate neurotrophin and immune signaling interactions in MDD [101]. The effects of DIO on the hippocampus have received considerable attention because of the well-reported effects of HFD to elicit cognitive and emotional impairments [102]. Among them is disrupted neurogenesis in the hippocampus, a key structural alteration involved in depression and antidepressant responses. High-fat feeding triggers hippocampal proinflammatory marker upregulation that can elicit depressive-like behavior, reduce neurogenesis, and impair hippocampal function [102]. Microglia contribute to this process by suppressing neuronal stem cell proliferation and inhibiting survival of new neurons and their integration into neuronal circuits [103]. Neuroplastic adaptions to obesity also extend to other structures controlling mood, such as the prefrontal cortex. Both obesity and depression share similar morphometric anomalies in medial prefrontal cortex [104], and chronic HFD exposure in rodents, leading to obesity, gives rise to impairments in prefrontal cortex-dependent functions that are accompanied by changes in dendritic spine density and synaptic remodeling [105]. Adolescence is considered a sensitive period for prefrontal cortex functional modulation by obesity, as HFD can inhibit prefrontal cortex synaptic plasticity to induce local perturbations in excitatory transmission in adolescent mice [106].

Numerous rodent studies emphasize neurotrophic factor signaling in the excitability of medium-spiny neurons of the striatum in the onset of depressive behavior. Changes in neurotrophic signaling are deemed to affect neurotransmitter levels (see later) and to be downstream of changes in transcriptional activity, including increased nucleus accumbens NFκB transcription that has been observed in response to repeated stress [107] and chronic high-fat feeding [34], leading to depressive and anxiety-like behaviors. In addition, elevations of phosphorylated CREB within the nucleus accumbens produces signs of anhedonia and behavioral despair in rodents [107] and are observed after chronic consumption of a HFD [28]. Brain-derived neurotrophic factor is a downstream target of CREB and elevated brain-derived neurotrophic factor expression is implicated in the morphological changes in nucleus accumbens neurons. Brain-derived neurotrophic factor has been widely studied in hippocampus and frontal cortex for its role in depression, where a decline in brain-derived neurotrophic factor levels is associated with cognitive deficits caused by HFD [108]. In contrast, increasing brain-derived neurotrophic factor in the nucleus accumbens or ventral tegmental area produces a depressive-like phenotype, whereas animals with selective knockout of brain-derived neurotrophic factor in ventral tegmental area are protected from depressive effects produced by social defeat stress [107]. Brain-derived neurotrophic factor protein levels in the nucleus accumbens and both brain-derived neurotrophic factor and pCREB levels in the dorsal striatum correlate with the degree of HFD-induced behavioral despair in mice. Enhanced signaling of both CREB and brain-derived neurotrophic factor in the nucleus accumbens could be a risk for depression and increased food-seeking observed in obesity with immunometabolic dysfunction.

Monoamine imbalances

Monoamine neurotransmitter perturbations are a recognized feature of both depression and obesity. Offset by common antidepressants [selective-serotonin reuptake inhibiters (SSRI)], blunted serotoninergic tone has been extensively associated with mood and emotional deficits [109]. Altered neurotransmitter levels observed in depression are, in part, a consequence of changes in transcriptional activity and neurotrophic signaling in response to internal and external stressors. Cytokines are a key mediator of such adaptations and can contribute to changes in the synthesis, release, and degradation of neurotransmitters and thereby promote changes in neuronal excitability. Chronic HFD in male mice, leading to increased anxiety-like behavior, has been shown to impair the basal electrical activity and excitability of serotonin neurons as well as serotonin-mediated neurotransmission in the hippocampus [33,35]. Similarly, obesity-induced increases in neuroinflammation were recently shown to suppress serotonin signaling by increasing its clearance from the synaptic cleft in the hippocampus [110], findings that provide a potential synaptic mechanism for reduced SSRI responsiveness in obese individuals with depression. The kynurenine pathway is well-implicated in the interaction between immune responses and serotonin neurotransmission. Inflammatory cytokines and their signaling pathways can activate the enzyme indoleamine 2,3 dioxygenase (IDO), which converts tryptophan, the primary amino acid of serotonin, into kynurenine, thus potentially depleting the availability of serotonin in the brain. Kynurenine affects neural afferents and circulating immune mediators that activate brain endothelial cells, astrocytes, and microglia via IDO, eventually altering synaptic glutamatergic neurotransmission (Figure 2). The influence of inflammation on IDO shifts kynurenine metabolism towards microglial byproducts, such as 3-hydroxykynurenine and quinolinic acid, a change associated with elevated oxidative stress and glutamate excitotoxicity that could contribute to depressive symptoms [111,112].

Blunted dopamine tone in the striatum has been consistently described in obese individuals and in rodent models of obesity [113]. DIO in rodents associates with reduced dopamine biosynthesis, turnover, and overflow and reduced dopamine receptor binding and signaling. Correspondingly, several lines of evidence point to hypodopaminergic states in MDD. Blunted mesolimbic dopamine signaling has been more directly implicated in anhedonia, a cardinal symptom of MDD that is ineffectively treated by SSRIs [114]. Animal models of depression that reliably induce anhedonia are associated with mesolimbic dopamine abnormalities [115]. As a link to obesity-associated depression, animals challenged with inflammatory cytokines (e.g., IL-1β and IFNα) have a decrease in striatal dopamine release, which correlates with anhedonia [61]. Together, modulation in corticolimbic serotonin and dopamine signaling in mood networks are associated with depression and anxiety emergence in obesity, although it remains poorly understood to what degree particular changes are causal or a consequence of mood and metabolic changes.

Endocrine modulators of mood

Several endocrine hormones have been implicated in the effects of obesity and metabolic syndrome to elevate the threat of anxiety and depression. As endocrine mediators of depression have been recently reviewed [116], this next section will be limited to obesity-associated changes in cortisol, insulin, and leptin signaling and their potential contribution to the manifestation of depression and anxiety in the obese state. It should be noted, however, that other hormones have been implicated, including adiponectin, resistin, and ghrelin, yet less is known about the direct effects of these hormones in brain regions underlying mood control.

HPA activation and stress-induced feeding

Heightened HPA activity is embodied in a broad spectrum of inflammatory, metabolic, and psychiatric diseases. Stressful life events can trigger depressive and anxiety episodes and early

life stress presents a particular risk for the development of clinical depression or anxiety disorders in adulthood [117]. The association between cortisol levels and obesity is complex [118]. Not all obese individuals have elevated cortisol and obesity development coincides with an increase in factors that enhance cortisol production, such as chronic stress, consumption of food high in sugar and fat, and reduced sleep [118,119]. In turn, hypercortisolism favors visceral adipose accumulation via local GC signaling actions. The increase in adipose-derived proinflammatory cytokines can have a stimulatory effect on the HPA axis, while cortisol feeds backs to weaken immune activation. However, chronic stress is associated with downregulation of GC receptor-mediated transcriptional activity, resulting in GC insensitivity and loss of anti-inflammatory feedback [120]. Visceral obesity and loss of muscle mass associated with hypercortisolism favor clinical parameters of metabolic syndrome and promote melancholic depression. However, depression and obesity comorbidity is often defined by atypical features; this is mostly associated with normal or lower cortisol levels [121]. It may be that interindividual variation in GC sensitivity, which is partly genetically determined, may cause higher vulnerability for atypical depression in obesity, yet the precise contribution of HPA activity remains to be established.

HPA activity may more reliably participate towards the obesity and mood comorbidities via the well-known effects of stress to stimulate intake of palatable, energy-dense (comfort) foods in a subset of individuals. HPA dysregulation contributes to weight gain in stressed individuals via the actions of cortisol to trigger palatable food intake through brain GC receptors, an effect that leads to reduced HPA activity and short-term relief of negative affective states [119]. The impact of stress and anxiety on food consumption seems to be different between men and women, with a higher consumption of sweets and fast food reported in stressed women than men [119]. These observations connect with the reciprocal relationship between obesity and depression: depression increases the odds of developing obesity. This is consistent with the overlap in brain structure and neurotransmitter systems controlling mood and emotions and motivation for food (see later) and the hyperphagic and weight-gain side effects of antidepressants. As palatable food craving is a predictor of eating and weight gain, it can mediate the relationship between chronic stress and BMI and thus may strengthen the link between mood impairment and obesity.

Insulin

In obese individuals, decreased insulin sensitivity correlates significantly with greater depressive and anxiety symptomology [122,123]. In turn, a high percentage of patients with depression exhibit insulin resistance [124]. These findings suggest that impairments in insulin signaling modify the brain networks controlling mood and raise the question of whether insulin resistance contributes to mood disorders. On the one hand, inflammatory cytokines are a major contributor to insulin resistance: elevated circulating insulin activates macrophages and can promote macrophage insulin resistance. On the other hand, diminished brain insulin signaling, which can be provoked by neuroinflammation, can blunt the antidepressant effects of insulin or insulin-sensitizing agents [125]. In support of this, reduced brain insulin signaling in brain regions controlling mood has been observed in animal models of DIO [126]. Deletion of insulin receptor in neurons or astrocytes was shown to promote the development of anxiety- and depressive-like symptoms [103,127]. Inhibiting insulin and IGF1 receptor signaling, specifically in the hippocampus and the amygdala, confers anxiety along with memory impairments [128]. In addition, insulin decreases the amplitude of excitatory currents onto ventral tegmental area dopamine neurons, effects which are blunted in DIO rats [129,130]. The direct effects of insulin to increase neurogenesis may also contribute to its antidepressant-like and procognitive properties [131]. Other studies described the impact of insulin on the activity of non-monoaminergic neurons in the prefrontal cortex and nucleus accumbens [126]. Indirect evidence also suggests that insulin impacts the serotonergic system and that insulin resistance, specifically in 5-HT neurons,

participates in the development of mood disorders [125]. Nevertheless, it is not clear yet whether the impact of insulin on these circuits plays a role in the control of mood and whether their alteration may induce mood disorders. More studies are necessary to fully characterize the impact of insulin in the circuits regulating mood and emotion.

Leptin

Plasma levels of the adipose-derived hormone leptin negatively correlate with symptoms of anxiety and depression in women and men [116]. In a consistent manner, leptin can suppress anxiety-like behavior [132–135] and behavioral despair [136] in mice. The anxiolytic action of leptin in mice has been tied to leptin receptor signaling in mesolimbic dopamine neurons [137,138], whereas its effects to inhibit behavioral despair are attributed to signaling actions in the hippocampus [139]. Leptin can also potentiate the antidepressant effect of SSRIs [140,141] and prevent LPS-induced depressive behavior [142]. While studies in humans are limited, treatment with a leptin analog (metreleptin) has rapid antidepressant effects in individuals with anorexia nervosa marked by very low leptin levels [143]. In a corresponding manner, leptin resistance can elicit depressive-like behaviors in rats [144] and is associated with atypical features of depression (increased appetite and weight) in humans [145]. Interestingly, CRP directly inhibits the binding of leptin to its receptors and blocks the ability of leptin to induce satiety and weight reduction in mice [146]. Central leptin resistance should thus be considered and evaluated further as a key consequence of obesity that causes and/or perpetuates depression and anxiety development.

Treatment options

Antidepressant medications serve as the standard line of treatment; however, these drugs can be ineffective and most augment the risk of weight gain [147]. An effective therapeutic intervention for severe obesity is bariatric surgery, which has been shown to improve or even eliminate common coexisting medical conditions, diabetes, hyperlipidemia, and hypertension. Meta-analyses show that bariatric surgery is also associated with a significant reduction in the prevalence and severity of depressive and anxiety symptoms. Several lines of evidence reveal that improving energy metabolism through combining approaches that include diet, psychotherapy, bariatric surgery, and/or diabetes treatment can have antidepressant efficacy in obese patients. For example, adding a dietary weight loss intervention and psychotherapy has been shown to enhance the efficacy of antidepressant medications in obese individuals [148]. A dietary approach that includes anti-inflammatory foods and supplements, such as those containing high EPA n-3 PUFA and probiotics, could help attenuate psychological stress in obesity [149,150]. There is also evidence showing the fast-acting antidepressant actions of ketamine involve decreases in IL-6 and TNFα [151]; thus, ketamine may prove useful for treating depression in obese individuals. Recent therapeutic developments for treatment-resistant depression include the use of implanted electrodes to deliver deep-brain stimulation to the neuronal networks controlling mood and motivation for food [152]. For example, deep-brain stimulation in the nucleus accumbens has been shown to be effective at reducing body weight in obese rodents and patients [153] and may offer superior weight-reducing and antidepressant effects when combined with bariatric surgery [154].

Diabetes medications exhibit promising antidepressant and anxiolytic actions [125]. Though their mechanism of action may rely on their ability to improve peripheral insulin signaling, it is noteworthy that these pharmacological agents cross the BBB, thus their beneficial effects on mood could be driven by the modification of biological pathways common to both diabetes and depression, such as anti-inflammatory or antioxidative properties. Improvement of insulin signaling in discrete brain areas is another possible avenue, as one could expect that antidiabetic drugs stimulate the neuronal activity of serotonergic, noradrenergic, and/or dopaminergic neurons. For instance, the

insulin-sensitizing drug metformin can elicit an antidepressant-like effect in HFD fed mice and this beneficial effect would rely on the increase in activity of serotonergic neurons in the CNS. In particular, it has been proposed that peripheral insulin resistance increases branch-chained amino acids that limit the reuptake of tryptophan through the BBB, thereby limiting serotonin synthesis in the hippocampus [35]. These collective findings suggest that diabetes treatments could be repositioned to improve both depressive symptoms and diabetes concurrently and perhaps as an add-on strategy to improve the efficacy of other antidepressant drugs.

Concluding remarks

The incidence of depression and anxiety in obese individuals has numerous mental and physical repercussions beyond encumbering psychological wellbeing. These include impairments in cognition that can aggravate mood and emotional dysfunction. Obese individuals and animal models of obesity present poorer performance on diverse cognitive tasks and these deficits are exacerbated in instances of comorbid depressive disorder [155]. While not covered here, another serious corollary of mood disorders is reduced voluntary and spontaneous physical activity, which can also be causal of obesity and cardiovascular disease and thereby aggravate mental health conditions. A sedentary lifestyle is a significant contributor to vascular pathology and inflammation, which favors reduced brain blood flow, nutrient absorption, and cellular proliferation to promote neuroinflammation along with mood and cognitive dysfunction. Although there is limited evidence for depression and obesity comorbidity, exercise has been shown to enhance mental health outcomes in obesity via ameliorating self-efficacy and autonomous motivation [156]. Lifestyle intervention strategies such as this could be combined with pharmaceutical compounds and/or surgical interventions to alleviate mood and emotional disturbances. New research developments uncovering the metabolic and neurobiological mechanisms by which obesity heightens the risk of depression and anxiety will prove valuable for evaluating new treatment strategies (see Outstanding questions).

Outstanding questions

To what degree do external stressors enhance the mental health risks of obesity? Are obese individuals more susceptible?

What is the relative contribution of obesity-induced inflammation originating from adipose tissue versus blood-borne and gut-derived inflammation to neural function?

What is the sequence of events that generates structural and functional changes in mood networks? Do direct brain nutrient actions initiate the neuroinflammatory cascade?

Which brain nutrient receptors and transporters influence neuroimmune function and mood states?

Why are brain regions controlling mood and cognition more affected by metabolic dysfunction? Does poor diet and obesity cause specific impairments to the BBB surrounding corticolimbic structures?

How can we better expand public knowledge of the importance of healthy diet and implement economic and public policies that facilitate intake of anti-inflammatory foods or supplements?

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Declaration of interests

No interests are declared.

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