The potential biological mechanisms of obesity effects on depression: A systematic review of the literature and knowledge mining

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ABSTRACT

Depression and obesity (BMI ≥ 30) have been recognized as major public health issues worldwide. Although they have traditionally been compartmentalized as separate physical and emotional health conditions, evidence has suggested interactions and common pathways between them, implying that they probably shared common underlying biological mechanisms. By a systematic review of the literature and knowledge mining, we explore a potential biological mechanism of obesity effects on depression. Bioactivators in the body of obesity including adiponectin, leptin and its receptors, ghrelin, endocannabinoids and orexin receptors may contribute to depression by the hypothalamic pituitary adrenal axis, psycho-neuro-immunological system, neurovegetative system and brain areas control of mood and emotion such as hippocampus, cortex and amygdala.

Keywords: Obesity; Depression; Biological Mechanisms; Literature and Knowledge Mining

1. INTRODUCTION

Obesity is an increasingly prevalent public-health problem with significant costs in the form of disease and premature death [1], increased health-care costs [2], and social stigmatization [3]. In addition, obesity causes or exacerbates many health conditions, both independently and in association with other diseases [1]. Recent data from the National Physical Fitness Monitoring in China in 2010 indicate that approximately 32.1% of adults and 39.8% of older Chinese are obese. Physical complications from obesity have been studied extensively, especially coronary heart disease, certain forms of cancer, and type 2 diabetes [4]. However, less is known about the relationship between obesity and major depressive disorder.

For the most part, obesity and depression have been compartmentalized as separate health problems of a physical and emotional nature, respectively [5]. However, the fact that depression and obesity have shared symptoms such as sleep problems, sedentary behavior and dysregulated food intake is not a mere coincidence but appears to be related to shared pathophysiological mechanisms. The purpose of the present article is to review the physiological and biochemical changes induced by depression and obesity in the body, highlight similarities in their biological presentation, review and speculate common pathways or other connecting mechanisms.

2. METHODS

Amounts of Medline, PsycINFO, PubMed, and Web of Science searches were conducted using the key words metabolic syndrom, waist circumference, waist hip ratio, obesity, overweight, central adiposity/obesity, visceral adiposity/obesity, body fat distribution, psychological, depression/major depressive disorder. After a systematic review of the literature, the method of noninteractive literature-based knowledge discovery created by D. R. Swanson was used to search the relative literature between obesity and depression by a man-computer interactive system named as Arrowsmith. The process starts with a given A and C. It retrieves all literature containing either
versely, i.c.v. administration of exogenous adiponectin injection of an adiponectin neutralizing antibody pre-

social interaction time and intracerebroventricular (i.c.v.) model of depression, which correlates with decreased 

elevations in plasma are reduced in a chronic social-defeat stress play a role in developing of depression. Adiponectin lev-
elations have also been shown to correlate inversely with anxiety scores, a condition highly 

adiponectin hypothesis about psychopathology in the 

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between decreased plasma adiponectin concentration and 

adiponectinemia. Moreover, circulating adiponectin levels have been shown to correlate inversely with anxiety 

scores by the pathway of Psycho-neuro-immunological aspects [12]. 

Adiponectin may regulate the expression of several pro- and antiinflammatory cytokines and reduce both secretion and attenuate the biological effects of TNF-a [20,21] and to induce the production of antiinflammatory cytokines such as interleukin-10 (IL-10) and interleukin-1 receptor antagonist (IL-1RA) [22]. Proinflamma-
tory mediators such as IL-6 can regulate the expression of adiponectin by way of suppressing adiponectin transcription and translation [23], and contrarily, weight loss is a potent inducer of adiponectin synthesis which might lead to dysregulation of the controls that inhibit the production of proinflammatory cytokines, thereby leading to the production of increased levels of proinflammatory mediators [24]. The hypothalamic pituitary adrenal (HPA) axis also plays a role in adiponectin regula-
tion; adiponectin gene expression is reversibly down-
regulated by dexamethasone [23], and glucocorticoids have been shown to inhibit adiponectin function [25].

3. RESULTS 

Although it seems obvious that obese people would likely be at higher risk for major depressive disorder (MDD) problems, the mediating factors in the relation-

ship between psychological problems and obesity are still not well established. In this section, we review the internal biological activities of the body that may serve as links between obesity and depression and possible targets for both disorders.

3.1. Adiponectin 

Adiponectin (also referred to as GBP-28, apM1, AdipoQ and Acrp 30) is a protein which in humans is en-
coded by the ADIPOQ gene [6]. It is involved in regu-

ating glucose levels as well as fatty acid breakdown, and a protein hormone that modulates a number of metabolic processes, including glucose regulation and fatty acid catabolism [7]. Adiponectin is exclusively secreted from adipose tissue and also from the placenta in pregnancy into the bloodstream and is very abundant in plasma relative to many hormones [8]. Levels of the hormone are inversely correlated with body fat percentage in adults. The hormone plays a role in the suppression of the metabolic derangements that may result in type 2 diabetes [9], obesity, atherosclerosis [7], non-alcoholic fatty liver disease (NAFLD) and an independent risk factor for metabolic syndrome [8]. 

A epidemiological studies documenting an association between decreased plasma adiponectin concentration and an increased risk of MDD were published [10]. And the adiponectin hypothesis about psychopathology in the context of obesity was proposed [11]. Moreover, circulating adiponectin levels have also been shown to correlate inversely with anxiety scores, a condition highly comorbid with depression [12]. 

As an adipokines, adiponectin has been believed to play a role in developing of depression. Adiponectin levels in plasma are reduced in a chronic social-defeat stress model of depression, which correlates with decreased social interaction time and intracerebroventricular (i.c.v.) injection of an adiponectin neutralizing antibody precipitates stress-induced depressive-like behavior. Conversely, i.c.v. administration of exogenous adiponectin produces antidepressant-like behavioral effects in normal-weight mice and in diet-induced obese diabetic mice [13]. Results of studies examining adiponectin in clinical populations have been variable. The original work about the links reported a decrease in plasma adiponectin concentrations in symptomatic patients with MDD [10] and an increase in adiponectin in patients with depression that was successfully treated [14], other studies have been unable to find changes in people with depression [15-17]. This effect may be mediated by antidepressants in the short-term [18] and weight gain over time [19], but recent work suggests that the presence of weight gain and depression also appears to be additive. The two conditions appear to have a greater effect on adiponectin that either does separately, indicating that an underlying vulnerability may be conferred and then compounded by either of the two conditions and their resultant hypoadi-
ponectionemia. Moreover, circulating adiponectin levels have been shown to correlate inversely with anxiety scores by the pathway of Psycho-neuro-immunological aspects [12]. 

Leptin is a peptide hormone secreted from adipocytes, circulates in the blood as a 16-kDa protein and enters the brain by a saturable transport mechanism. Leptin has been well-recognized as an adiposity negative feedback signal and a critical mediator of energy homeostasis since its discovery. Leptin receptor is a single mem-
brane-spanning protein that belongs to the class I cyto-
kine receptor superfamily. Accumulating evidence has expanded the function of leptin from the control of en-
ergy balance to the regulation of other physiological processes such as reproduction and cognition [26,27]. Supporting this notion, the leptin receptor is widely dis-
tributed in discrete brain regions. Particularly, LepRb, an
isoforms of the leptin receptor, is highly expressed in brain areas implicated in the control of mood and emotion such as the hippocampus, cortex and amygdala.

Animal models of depression in rats or mice exposed to chronic unpredictable stress or chronic social defeat stress to develop behavioral deficits and endocrine abnormalities, mimicking the symptoms of human depression, showed decreased basal levels of leptin in plasma [28]. It was hypothesized that leptin insufficiency may underlie depression-like behavioral deficits [29]. One of the depression-like behaviors in chronically stressed animals is reduction of sucrose preference, which is regarded as an analog of anhedonia, a key symptom of depression in human [30]. Systemic administration of leptin can reverse the chronic stress-induced decrease in sucrose preference [28].

Studies about the role of leptin signaling in human depression is limited and controversial [31,32]. With larger sample sizes, researchers demonstrated that plasma leptin levels were decreased in patients with major depression independent of body mass status [33,34]. Also, lower levels of leptin in cerebrospinal fluid were found in suicide attempters with depression than those without depression [35,36]. These suggest a link between reduced leptin levels and major depression. It has been reported that obese people are approximately 20% more likely to have depressive disorders than non-obese subjects [37], and leptin resistance is caused by defects in the leptin signaling pathway possibly at several levels, including impaired transport of leptin across the blood-brain-barrier, reduced function of the leptin receptor and defects in leptin signal transduction [38].

The principal homeostatic site of action of leptin and ghrelin is the hypothalamic arcuate nucleus, where they exert anorexigenic or orexigenic effects, respectively, through a biologically elegant system of neuropeptides. Interestingly, receptors for leptin and ghrelin, as well as receptors for other feeding peptides are expressed in several depression-related limbic substrates [39]. In light of leptin’s ability to inhibit depressive behaviors in animal models, it is possible that leptin resistance may contribute to the higher rate for depression in obese people. This could also help to interpret some of the conflicting results obtained in relation to circulating leptin levels in depressed patients [40].

3.3. Ghrelin

Ghrelin is a natural ligand for the growth hormone (GH)-secretagogue receptor (GHS-R), is primarily produced in the stomach. Ghrelin plays a critical role in a variety of physiological processes, including the stimulation of GH secretion and regulation of energy homeostasis by stimulating food intake and promoting adiposity via a GH-independent mechanism [41,42].

Prior studies found that rises in ghrelin occur not only in response to states of energy insufficiency [43-45] but also following Anxiety and depression [46], and elevations in either gastric ghrelin mRNA or total plasma ghrelin have been observed in response to various models of acute stress, including following a tail pinch stress protocol in ddY mice and following a water avoidance stress protocol in Wistar Kyoto and Sprague-Dawley rat [47,48].

Mouse models has revealed that increasing circulating ghrelin levels by 10 days of calorie restriction or by acute s.c. injection produces antidepressant-like responses in the forced swim test, but caloric restriction no longer induced these responses in mice lacking ghrelin receptors (GHSRnull mice), thus suggesting that interference with ghrelin signaling negates the antidepressant-like behaviors associated with calorie restriction [46]. Also, upon challenge with the chronic social defeat stress (CSDS) protocol, GHSR-null mice manifested greater social isolation (another marker of depression-like behavior) than did wild-type littermates. Thus, it has been suggested that activation of ghrelin signaling pathways in response to chronic stress may be a homeostatic adaptation that helps individuals cope with stress.

Studies has demonstrated the hippocampus as being involved in antidepressant efficacy and other aspects of depression, including that associated with stress, and the hippocampus together with the neocortex mediates cognitive aspects of depression such as memory impairment and feelings of worthlessness, hopelessness, guilt, and suicidality [49]. Interestingly, GHSRs are known to be expressed within all regions of the hippocampus [50,51]. In addition, peripherally administered ghrelin is taken up by and increases spine synapse density within the hippocampus [52]. Ghrelin also recently has been shown to stimulate cellular proliferation and differentiation of adult rat hippocampal progenitor cells [53,54], thus suggesting that ghrelin also might induce hippocampal neurogenesis.

3.4. Endocannabinoids

Endocannabinoids are lipid mediators derived from membrane phospholipids or triglycerides with complex effects on body weight and metabolic regulation [55,56]. Endocannabinoids in tissues controlling energy homeostasis are altered in obesity, and has been suspected to contribute to the association of visceral fat accumulation with metabolic diseases. The endocannabinoid system, which exists in both the brain and the periphery, is both a regulator and effector of the stress response [57,58]. Preclinical studies have demonstrated that the contents of the endocannabinoids in limbic and hindbrain regions are regulated by a variety of stressful stimuli [57]. These
changes in endocannabinoid activity dampen or promote recovery of the hormonal stress response since endocannabinoid signaling negatively modulates the sensitivity and output of the hypothalamic-pituitary-adrenal (HPA) axis [57,58].

Prior study demonstrated that exposure of humans to an acute social stressor results in altered circulating concentrations of the endocannabinoids [59,60], the source of circulating endocannabinoids is not well characterized, but adipocytes, endothelial cells and macrophages, as well as visceral organs, such as the liver and intestines, all possess the ability to synthesize and release endocannabinoids into the blood [61-63]. Previous findings of a reduction in circulating endocannabinoid content in an independent population diagnosed with major depression were replicated [62].

Endocannabinoid signaling is known to influence mood and emotion, such that impairments in endocannabinoid signaling can produce depressive-like and anxiety-like symptoms in rodents [60] and administration of CB1 receptor (G-protein coupled receptors) antagonists to humans has been found to increase indices of depression and anxiety [63]. Accordingly, the deficit in circulating endocannabinoids documented in individuals with major depression may contribute to the emotional sequelae associated with this disease.

3.5. Orexin Receptors

Orexin-A and orexin-B, via their receptors orexin-1 receptor (OX1R) and orexin-2 receptor (OX2R) have been shown to play a role in the regulation of feeding, body weight, and energy expenditure. The orexigenic peptides, orexin-A and orexin-B, are proteolytically cleaved from a common precursor, prepro-orexin and share 46% amino acid sequence identity [64,65]. The neurons producing orexins are located in the lateral and posterior hypothalamus and send their projections widely into the central nervous system, resulting in multiple physiological functions, including the control of arousal and sleep-wake cycle, regulation of cardiovascular and autonomic function, and the neuroendocrine system [66-68]. Orexins bind to and activate two G-protein-coupled receptors, orexin-1 receptor (OX1R) and orexin-2 receptor (OX2R), which display 64% amino acid sequence identity [67]. Orexin-A binds with a high affinity to OX1R, whilst OX2R binds both orexin-A and orexin-B with similar affinity. Studies have demonstrated that the orexin receptors distributes in human isolated adipocytes [69] and non-central tissue distribution include the adrenal gland [70], male reproductive system [71] thyroid, lung, kidney, and jejunum [72].

Calorie restriction and subsequent weight loss in mammals induces a wide array of behavioral responses directed toward promoting the identification of new food sources. These responses have been well studied in mice and include increased arousal, increased locomotor activity, and decreased anxiety-like behavior [73-75]. Interestingly, several psychiatric disorders, notably “typical” major depressive disorder and anorexia nervosa, are characterized by reduced calorie intake. Behavioral responses to calorie restriction are thought to mediate certain clinical aspects of the illness. For example, reduced production of leptin by adipose tissue has been implicated in the increased psychomotor activity of patients suffering from anorexia nervosa [76].

Findings demonstrated significant downregulation of prepro-orexin mRNA expression after chronic social defeat stress. Interestingly, decreased levels of orexin-A were reported in the CSF of suicidal patients with major depressive disorder [77], supporting chronic social defeat stress as a model of major depression. One interesting possibility is that prolonged reduction in orexin signaling may contribute to the development of neurovegetative symptoms seen in major depression. Orexin neurons have broad projections, and multiple functions have been attributed to orexin signaling, including consolidation of arousal, regulation of metabolism, food intake, and cardiovascular responses, controlling fluid intake, and mediating food and drug reward responses [78-81]. Given the multiple roles of orexin neurons, reduction in orexin signaling makes an attractive candidate to explain the disrupted sleep/wake cycles, altered appetite, and psychomotor retardation often observed in depressed patients.

4. DISCUSSION

The complex relationship between obesity and depression had been reported based on only one bioactivator in most of prior studies. This review as well as knowledge mining discusses a potential biological mechanism of obesity effects on depression systemly. Bioactivators in the body of obesity including adiponectin, leptin and its receptors, ghrelin, endocannabinoids and orexin receptors may contribute to depression by the hypothalamic pituitary adrenal axis, psycho-neuro-immunological system, neurovegetative system and brain areas control of mood and emotion such as hippocampus, cortex and amygdala.

Adiponectin plays a role in the suppression of the metabolic derangements and the levels of which are inversely correlated with body fat percentage and anxiety scores. The biological mechanism may be that obesity results in the decrease of plasma adiponectin concentration and then increases the risk of MDD by HPA axis and psycho-neuro-immunological system. As an adiposity negative feedback, leptin is a critical mediator of energy homeostasis. The decreased plasma leptin level will contribute to depressive behaviors through a biological
system of neuropeptides. The rises in ghrelin occur following depression, and the points of action may be regions of hippocampus. Endocannabinoid is an important mediator of energy homeostasis and a regulator and effector of the stress response. The biological mechanism may be that depression leads to the rise of endocannabinoids, then the fat accumulation and subsequent to come into be obesity. Orexin produced by neurons is located in hypothalamus. Weight loss will induce a behavioral response of food intake and this response will decrease anxiety-like behavior through the neurovegetative system.

The method of noninteractive literature-based knowledge discovery contributes to exploring the relation between psychological characteristics and illness, and the theoretical hypothesis of biological mechanism can be constructed between them through a system literature review to provide valuable reference for medical and psychosocial researchers to benefit mental diseases understanding and disease prevention and control.

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