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REVIEW

Peptides from adipose tissue in mental disorders

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Abstract

Adipose tissue is a dynamic endocrine organ that is essential to regulation of metabolism in humans. A new approach to mental disorders led to research on involvement of adipokines in the etiology of mental disorders and mood states and their impact on the health status of psychiatric patients, as well as the effects of treatment for mental health disorders on plasma levels of adipokines. There is evidence that disturbances in adipokine secretion are important in the pathogenesis, clinical presentation and outcome of mental disorders. Admittedly leptin and adiponectin are involved in pathophysiology of depression. A lot of disturbances in secretion and plasma levels of adipokines are observed in eating disorders with a significant impact on the symptoms and course of a disease. It is still a question whether observed dysregulation of adipokines secretion are primary or secondary. Moreover findings in this area are somewhat inconsistent, owing to differences in patient age, sex, socioeconomic status, smoking habits, level of physical activity, eating pathology, general health or medication. This was the rationale for our detailed investigation into the role of the endocrine functions of adipose tissue in mental disorders. It seems that we are continually at the beginning of understanding of the relation between adipose tissue and mental disorders.

Key words: Adiponectin; Leptin; Visfatin; Resistin; Omentin; Adipsin; Eating disorders; Schizophrenia

Core tip: New approach to adipose tissue as endocrine organ developed new research fields in psychiatry. Several papers linked the well-known adipokines like leptin, adiponectin and resistin with mental disorders. But there are still a hundreds of recently discovered adipokines with possible role in mental disorders.

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INTRODUCTION

This year is the twenty-year anniversary of a new approach to adipose tissue. Since the discovery of leptin[1] in 1994, adipose tissue has been recognized as an endocrine organ and an important source of biologically active peptides called adipokines.

There is growing body of clinical evidence that adipokines play a role in various mental disorders including schizophrenia, mood disorders, anxiety disorders, post-traumatic stress disorder, eating disorders (EDs), sleep disorders, autism spectrum disorders (ASDs), attention deficit hyperactivity disorder and some neurodegenerative disorders such as Alzheimer's disease (AD)[2-6]. Research on adipokines has looked at the effects of drugs used to treat mental disorders on the plasma level of adipokines, the role of adipokines in the etiology of mental disorders and mood states and their impact on other aspects of the health status of psychiatric patients. One of the most interesting and challenging areas of research is the role of adipocytes in the etiology of mental disorders. Recently clinical research has been corroborated by novel studies in animal models. Use of animal models enables us to develop a more sophisticated causal model of the role of adipocytes in normal and pathological psychological functioning. Several types of adipocyte receptor have been found in several central nervous system areas, and have been shown to affect brain function through neuroplastic processes[7-9]. These findings in depth the immune theory of psychiatric diseases[10,11]. Also some hypotheses tiding etiology of mental disorders and addictions in adults with disturbed adipocyte development in childhood were formulated[10-12]. There are other possible mechanisms by which adipocytes may be involved in the etiology of mental disorders[13,14]. At present the evidence is inconsistent, and raises new questions and suggests new topics for research[15]. Understanding the role of adipocytes in the etiology of mental disorders might lead to new treatments and approaches to managing mental health problems[16-19]. On the other side research on the role of adipokines in mental health reflects significant changes in perception of adipose tissue. Methodological problems with research in this area continue to be reflected in inconsistent results[20-27]. In attempting to synthesize the findings of the various studies it is essential to consider interactions among factors such as patient age, sex, socioeconomic status, smoking habits, level of physical activity, eating pathology, general health and medication. More research is needed, particularly into the ways in which adipokines circulate around the various body fluids and compartments[10]. This review discusses research linking selected adipokines with mental disorders.

ADIPONECTIN

Adiponectin is a 244-amino acid peptide produced in adipose tissue by mature adipocytes and is classed as an adipokine. Adiponectin was discovered independently in four different laboratories in 1995; it is also known as adipoQ, adipocyte complement-related protein with mass = 30 kDa, gelatin binding protein with mass = 28 kDa and adipose most abundant gene transcript 1 (apM1)[28]. Native adiponectin creates homotrimers that may form dimers, trimers and high molecular weight (HMW) complexes[29]. Adiponectin interacts with adiponectin receptors (AdipoR1 and AdipoR2) and is homologous to C1q subunits and globular domains of type X and Ⅷ collagens[30]. Both receptors are expressed in white and brown adipose tissue[31]. AdipoR1 is expressed mainly in skeletal muscles but is also found in endothelial cells. It has high affinity for globular adiponectin and low affinity for full-length adiponectin[32]. The complex of AdipoR1 with adiponectin activates AMP-activated protein kinase (AMPK) and promotes lipid oxidation[32]. AdipoR2 is highly expressed in the liver and has intermediate affinity for both globular and full-length adiponectin. It increases peroxisome-proliferator-activated receptor ligand activity by reducing steatosis and enhancing insulin sensitivity through activation of AMPK[24]. T-cadherin, an adiponectin-binding protein with high affinity for HMW adiponectin multimers is mainly expressed in the endothelium and smooth muscle[33].

BIOLOGICAL ROLE OF ADIPONECTIN

The biochemical effect of adiponectin partly depends on the relative high concentration of this peptide in the blood, as compare to the remaining adipokines[34,35]. Adiponectin accounts for approximately 0.01% of all plasma protein[36]. Adiponectin is mainly involved in energy homeostasis. It is exclusively secreted by adipocytes and is linked to glucose and lipid regulation[37]. Adiponectin stimulates fatty acid oxidation, suppresses hepatic gluconeogenesis and also inhibits monocyte adhesion, macrophage transformation, proliferation and migration of smooth muscle cells into blood vessels[29]. These metabolic and anti-inflammatory actions are closely associated with activation of AMPK and modulation of nuclear factor-B. AdipoR1 and AdipoR2 are expressed widely both in peripheral tissues and in the brain[38]. Adiponectin plays a crucial role in several metabolic diseases. It has strong insulin-sensitizing and anti-inflammatory effects. Multiple metabolic abnormalities such as obesity, diabetes and atherosclerosis have been associated with decreased adiponectin levels[39]. In several animal models treatment with adiponectin was shown to reverse these abnormalities, resulting in increases in fatty acid oxidation, insulin sensitivity and reductions in glucose and lipid levels[40].

ADIPONECTIN IN MENTAL DISORDERS

Adiponectin activity is strongly associated with metabolic disorders and energy expenditure interactions, but it has also been associated with various mental disorders such as mood disorders, anxiety disorders, eating and sleep

disorders and neurodegenerative disorders.

Decreased serum adiponectin levels have been also reported in major depressive disorders, panic disorders and schizophrenia[41-43]. Serum levels of adiponectin were significantly lower in elderly patients with major depressive disorders than in non-depressed controls[44,45]. Adiponectin also plays an important role in depression-related behaviors. Circulating adiponectin levels were decreased in a chronic social defeat stress model of depression; they were also inversely correlated with the social interaction ratio. Adiponectin insufficiency increased susceptibility to stress-induced depressive behaviors and impaired function of hypothalamic-pituitary-adrenal axis[46]. Expression of AdipoR1 and AdipoR2 was high in areas of the brain involved in depressive disorders and intra-cerebral administration of adiponectin elicited antidepressant-like behavioral effects in normal-weight mice and obese diabetic mice[47].

Reduction in circulating adiponectin levels has been correlated with social withdrawal, which is common in psychiatric disorders such as depression and post-traumatic stress disorder. The mechanisms underlying the reduction in circulating adiponectin levels induced by social defeat are still not known, however very recent research has shown that glucocorticoid stress hormones inhibit adiponectin gene expression and secretion *in vitro* and *in vivo*[48,49]. It seems reasonable to speculate that a social defeat-induced decrease in plasma adiponectin levels may be connected to a stress-induced surge in glucocorticoids[47].

The data on adiponectin levels in anorexia nervosa (AN) patients are inconsistent. It has been reported that adults with AN have decreased[20], increased[21,22] or unchanged[23] adiponectin levels. Earlier research showing that obese patients have lower total adiponectin levels suggested that adiponectin levels might be negatively correlated with body mass index (BMI)[29]. A later study assessing levels of specific isoforms of adiponectin found that percentage HMW was lower in the AN group than in controls, whereas percentage low molecular weight (LMW) was higher in the AN group. HMW and LMW were positively and negatively correlated with the BMI respectively in the sample as a whole. The observation that the level of total adiponectin was similar in the AN group and control group suggests that AN may be associated with upregulation of adiponectin production, because these patients with AN appear to have produced a similar amount of adiponectin to controls despite having fewer fat cells[50].

Assessments of adiponectin levels in patients with schizophrenia suggest that they are dependent on nutritional status. Elevated adiponectin levels were observed in normal-weight, drug-naïve, first-episode schizophrenia patients. In schizophrenia upregulated secretion of adiponectin has been correlated with levels of pro-inflammatory mediators[13]; it has been suggested that inflammation is not the only reason for the increase in adiponectin secretion in schizophrenia.

Although adiponectin is involved in sleep regulation and the pathomechanism of seizures normal levels have been reported in normal-weight patients with mild sleep disorders such as parasomnia and epilepsy[51]. Only in patients with severe sleep disorders such as obstructive sleep apnea hypopnea syndrome (OSAHS) have decreased levels of adiponectin been found, but OSAHS is associated with more serious hypoxia-related changes in the brain and frequently co-occurs with obesity[51].

Adiponectin abnormalities have been implicated in various metabolic disorders and may also be risk factors for the development of neurodegenerative disorders such as AD[52].

To date few studies have investigated the potential relationship between adiponectin and AD. One recent clinical study demonstrated that some AD patients have elevated levels of adiponectin in plasma and cerebrospinal fluid[53], which suggests that adiponectin may play an important role in mediating AD progression, possibly through its effects on peripheral or brain metabolism. Recent studies have shown that the adiponectin receptors AdipoR1 and AdipoR2 are expressed throughout the central nervous system[54]. But there is still controversy as to whether adiponectin crosses the blood-brain barrier[24,25]. It is likely that both adiponectin and adiponectin pathways could be targets for a new, effective treatment for AD[16].

LEPTIN

Leptin, a 146-amino acid peptide, is a product of the *Ob*(*Lep*) gene and is mainly synthesized by adipocytes. Leptin has also been extracted from placentae, stomach mucosa, enterocytes, liver and bone marrow[55]. Leptin was identified in 1994 and takes its name from the Greek *leptos*, meaning slim, fit. It functions as a "satiety signal" and is released by fat tissue and regulate food intake regarding to total fat tissue storage[7]. Leptin plays an important role in peripheral signaling, providing information about accumulated energy stores and thus playing a role in long-term regulation of the amount of food ingested[7]. This adipose tissue-derived hormone modulates a complex hypothalamic network of several cooperating orexigenic and anorexigenic neuropeptides to reduce food intake and increase energy expenditure[56]. The arcuate nucleus (ARC) is an important leptin-sensitive hub. Other hypothalamic and thalamic nuclei including the paraventricular nucleus, dorsomedial nucleus, ventromedial nucleus and lateral hypothalamic area are also direct targets of leptin[57].

BIOLOGICAL ACTIONS OF LEPTIN

Leptin plays a critical role as a negative regulator of food intake through specific neuronal receptors localized in hypothalamic nuclei. Leptin stimulates anorexigenic neurons expressing pro-opiomelanocortin and inhibits orexigenic pathways releasing neuropeptide Y and the melanocortin antagonist Agouti-related peptide[58]. Leptin

serum concentrations are maintained in direct proportion to the fat tissue mass. In several animal models lack of leptin causes hyperphagia and obesity whereas leptin administration decreases body mass and increases energy expenditure[59]. However in humans 90%-95% of obese people have elevated leptin serum levels[60]. This suggests that obesity may be associated with problems with leptin signaling or dysregulation of the leptin-brain axis. Low serum leptin acts as a signal of lack of energy storage for hypothalamic regions; this function may have evolved as a defense against generalized metabolic debilitation[61]. In women a body fat percentage below 10%-15% is associated with cessation of menstruation and relative lack of leptin or leptin receptor dysfunction[62]. In adolescent girls and boys leptin stimulates higher release of hypothalamic gonadoliberin and-*via* specific receptors in the pituitary gland-follicle-stimulating hormone and luteinizing hormone (LH)[8]. Leptin also plays a crucial role in many physiological processes including angiogenesis, inflammation, immune function and reproduction[63].

LEPTIN AND MENTAL DISORDERS

In humans, both high and low levels of leptin have been associated with psychopathology. Leptin resistance accompanying obesity is supposed to influence disorders such as anxiety, depression and may affect neurocognitive functions[64]. At present it is commonly believed, although there is no definitive proof, that appetite modulators also affect non-homeostatic cognitive, emotional and reward factors involved in regulation of food intake[65,66]. The most common disorders associated with disturbance of metabolic state regulators are AN and bulimia nervosa (BN). AN and BN are classified as EDs of complex and still unknown etiology. AN is characterized by low leptin levels. Data on leptin levels in leptin in the BN are inconsistent; it is possible that leptin levels may be vary according to the phase of the disease or the severity of symptoms (overeating, compensatory behaviors)[67]. In underweight AN patients levels of leptin in plasma and cerebrospinal fluid are significantly lower than normal and correlated with BMI[68,69]. Leptin levels were similar in restrictive and binging/purging AN, suggesting that cachexia plays an important role in leptin changes in anorexia[70].

Hypoleptinemia is believed to be the primary signal for initial somatic and behavioral adaptations to starvation[71]. Recent research has focused on the potential influences of leptin and other hormones, severe life events and chronic stress in the onset and the course of EDs[46]. Leptin influences energetic balance but it also regulates processing of the hedonic and motivational components of rewards[72]. It is widely recognized that anhedonia, the inability to experience pleasure, is a key symptom of EDs[73,74]. Data from animal models has shown that food abundance increasing body weight as well as leptin levels suppress reward-related behaviors. Conversely caloric restriction and body mass reduction resulted in a decrease in leptin levels and an increase in reward-related behaviors[75]. Thus in line with these animal studies, similar observations have been recognized in chronically fasting patients with AN. The modulatory effect of leptin on reward-related behaviors has also been postulated to play a role in excessive exercising in AN patients[67]. Low leptin levels have been shown to correlate with hyperactivity in starved animals[76]. Amenorrhea, which is one of the most common symptoms of AN in female patients, is probably secondary to the decrease in adipose tissue, but may be directly associated with very low serum leptin levels[77]. It has been shown that a serum leptin level less than 1.85 mcg/L predicts amenorrhea and subnormal serum levels of LH in AN[78]. Weight restoration therapy does not reverse amenorrhea in all patients and it has been reported that in these cases leptin levels remain lower than in healthy controls[79]. Comorbid depressive symptoms are another characteristic of AN. Evidence indicates that there is a bidirectional relationship between depression and metabolic dysregulation[80,81]. Leptin receptors have been found in the limbic system, and leptin also has been shown to affect hippocampal and cortical structures through its effects on neurogenesis, axon growth, synaptogenesis and dendritic morphology. Low levels of leptin are associated with depressive behaviors and exposure to chronic stress decreases serum leptin. A recent study of therapy for AN reported a reduction in depressive symptoms measured with Beck Depression Inventory and Hamilton depression Rating Scale following increases in BMI and leptin serum levels. This suggests that there may be a direct association between leptin concentration balance and depressive symptoms[9]. Leptin may serve as biomarker for depression in general, or in depressed patients with altered metabolic function[82].

Modern research on the importance of leptin in EDs has explored its wider role, focusing on the critical role that appetite regulation and weight regulation mechanisms play in weight loss and maintenance of lean body mass in AN[83]. This research is aimed at understanding the ways in which leptin is transported to the brain and subsequent alterations in hypothalamic expression of leptin receptors and downstream signaling pathways[14]. Research into early epigenic encoding of leptin-receptor interactions[84] is another promising new area of investigation.

Early research on the role of leptin in schizophrenia explored the impact of treatment with antipsychotics on leptin levels[85]. The relationship between leptin level and weight gain associated with neuroleptic drugs has also be investigated[86]. There have been many reports of altered levels of leptin in schizophrenic patients; some studies reported decreased serum leptin levels in schizophrenic patients, but others have found increased serum leptin levels in antipsychotic-naïve female patients with schizophrenia[26,27]. The neurobiological basis of schizophrenia is not fully understood but dopamine abnormalities in this disease have been extensively investigated[87,88]. On animal model there is postulated theory of increased dopamine level in nucleus accumbens

in schizophrenic rats. Leptin may modulate dopaminergic activity through leptin receptor-expressing neurons in the mesolimbic pathway[89]. It has been reported that leptin reduces mesolimbic dopaminergic activity and decreases dopamine levels in the nucleus accumbens[90,91]. This is consistent with studies which have reported a negative correlation between leptin levels and severity symptoms in schizophrenia[85] and may indicate that leptin is involved in negative feedback to counteract increased dopamine activity in the brain[91]. However other study noted higher plasma levels of leptin in schizophrenic patients than in healthy controls[92].

RESISTIN

Resistin was discovered in 2001; it is a peptide and is also known as adipose tissue-specific secretory factor or C/EBP-epsilon-regulated myeloid-specific secreted cysteine-rich protein (XCP1). It is considered a pro-inflammatory factor and is thought to be responsible for resistance to insulin[93]. Adipocytes are the main source of resistin in the human body, but expression of resistin is also high in mononuclear blood cells.

Recently researchers suggested that there is an association between inflammatory agents produced by adipose tissue and risk of depression[11]. Some studies have reported a positive correlation between resistin concentration in the blood and atypical, melancholic subtypes of major depressive disorders[94,95]. This association may be related to the reduction in intrasynaptic concentration of monoamines by resistin *via* inhibition of release of norephinephrine and dopamine in the hypothalamus[96].

It has been suggested that resistin is involved in the pathogenesis of bipolar disorder (BD). Insulin resistance is one of the main etiological factors in BD. Resistin activates enzymes involved in gluconeogenesis and increases glycogenolysis, thereby contributing to hepatic insulin resistance by decreasing the expression of GLUT 4. A recent study reported increased levels of resistin in patients with BD, the specific role of resistin in the pathogenesis of the illness is still unknown[97]. Reduced concentration of resistin have been observed in patients with obsessive compulsive disorder[98], similarly lower levels of serum resistin have been observed in patients with ASDs[99] and EDs[100]. Low resistin levels in EDs could be due to downregulation of mononuclear macrophage levels and/or a reduction in pro inflammatory processes[100].

OTHER ADIPOKINES

The well-known adipokines are discussed above, but there are over 600 less well-known adipokines which are extensively involved in human physiology and pathology. Some adipokines are involved in the regulation of metabolism (*e.g.*, dipeptyl peptidase 4, vaspin, visfatin, chemerin), others in the immune response [*e.g.*, adipsin, ASP, SAA3, interleukin (IL)-17D, colony-stimulating factors], inflammation (*e.g.*, IL-1β, IL-6, IL-8, IL-10, C-reactive protein, monocyte chemoattractant protein-1, osteopontin, progranulin, chemerin), hypertension (*e.g.*, angiotensinogen), cell adhesion (*e.g.*, plasminogen activator inhibitor-1), adipogenesis and bone morphogenesis (*e.g.*, bone morphogenetic protein-7), cell or tissue growth (*e.g.*, insulin-like growth factor-1, transforming growth factor beta, fibronectin, fibroblast growth factor 21, vascular endothelial growth factor) and many others functions[101-108]. Some adipokines have multidirectional actions or interplay with other molecules in a variety of functions. These data urgent to define their function and potential clinical relevance in health and disease, also in mental disorders.

Few attempts have been already done. There was no significant association between the concentration of circulating visfatin and presence of EDs[109,110]. Recent studies have shown reliance between starvation and decrease plasma level of adipsin, which suggests possible role of this peptide in etiology of AN[111]. Serum levels of omentin were normal in drug-naive patients with major depression[112]. These negative results should not dissuade researchers from investigating the role of adipokines in mental disorders.

CONCLUSION

The studies discussed here provide evidence that disturbances in adipokine secretion are important in the pathogenesis, clinical presentation and outcome of mental disorders. There is a consensus that leptin and adiponectin are associated with symptoms of depression. Changes in the physiology of appetite modulators in EDs play a pivotal role in motivated behaviors, reward processes and energy balance. Sometimes, as in AN, secondary downregulation of adipokines has a significant impact on the symptoms and course of a disorder. A better understanding of the endocrine function of adipose tissue would have a significant impact on understanding of mental disorders and would lead to more rational therapies for these diseases. There is a lack of research into the role of adipokines in different mental disorders; this is an area which warrants further research. Detailed investigation of links between adipokines and mental disorders is still a new topic in psychiatric research.

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