

# A Novel Approach to Obesity from Mental Function

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## Abstract

Obesity is well recognized as serious problem in the world. Regular exercise and modest food intake are the basic strategies for healthy body weight. Although, it is very difficult to lose weight and it is much more difficult to avoid weight regain. Recently, from basic and clinical studies, some part of this difficulty might be explained by impairment of central nervous system due to obesity. Indeed, mental function, such as cognitive impairment, depression, vulnerability to stress, wrong body image, low self-esteem and dysregulation of hedonic hunger contribute to development of obesity. The link between such mental disorders and obesity is likely to be bidirectional. Brain inflammation and imbalance of neuronal plasticity caused by dysregulation of metabolic signals are candidates which cause mental disorders associated with obesity.

**Keywords:** Obesity; Weight loss therapy; Mental function; Brain Inflammation; Hormone; Neuropeptides; Neuronal plasticity

## The Mechanisms of Weight Control

Animals including humans are able to maintain almost stable body weight due to regulatory system for energy expenditure and food intake. On the other hand, in human society, body shape varies from extremely thin, anorexia nervosa, to extremely fat, obesity. Body weight is determined by an interaction between genetic, environmental and psychosocial factors. There are physiological time points when humans increase their body weight, such as, while in growth phase, pregnancy, and aging. Obesity also arises when taking energy far above these physiological demands. Recent drastic increment of overweight and obese is mainly due to decrease physical activity and increase energy intake. Regular exercise and modest food intake are well recognized for weight control. The health and psychosocial benefits of sustained weight loss are well established, even though this knowledge is not sufficient to motivate long-term behavioral change. It is most important for weight loss therapy that motivation for weight control beyond motivation for food intake. The interaction of the hypothalamus, which is the classical homeostatic energy regulatory site, and extra-hypothalamic brain areas related to regulation of emotion, cognition, and reward are the main construction in regulation of food intake. Recently, vulnerability to stress, wrong body image, low self-esteem, and dysregulation of hedonic hunger which are determined by these brain areas, contribute to development of obesity. In this context, such mental function is now recognized as a pivotal player in the management of weight loss therapy.

## Mental Aspect of Obesity

In adults, high prevalence of mental disorders including cognitive impairment is observed in obesity [1-5]. Among mental disorders, eating disorders are often comorbid with obesity [6]. Especially, binge-eating disorder is thought to be present in 20-40% of obese patient [6]. Moreover, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV TR, obesity is categorized as eating disorder [7]. Some population of obesity is even characterized as mental disorder with “compulsive food consumption” similar to drug addiction. Recent functional Magnetic Resonance Image (fMRI) study suggests that anorexia nervosa, which might have opposite phenotype to obesity, might have motivation and reinforcement for starving and hedonic for hunger [8]. This result speculates that obesity might have motivation and reinforcement for consumption of palatable food and fear for hunger. This concept is supported by Meule et al. [8] who reported that prevalence of food addiction diagnoses differed between weight classes such that overweight and obese participants had higher prevalence than

normal weight participants [9]. These findings suggest the existence of “compulsive food consumption”. This “compulsive food consumption” is difficult to be modified, and even if weight loss is achieved, the neural plasticity “fixed” by palatable food leads individuals to crave more palatable food and thus substantially regain weight. Moreover, a weakened Top/Down inhibition signal for food cravings and inadequate sensing of ingested nutrients resulting in hyperphagia of obesity has been detected in fMRI studies [10].

Obesity is also associated with an increased risk of developing depression and a higher likelihood of current depression [11-14]. Most obese individuals tend to have higher scores in depression, and the projected increase in the rates of being overweight and obesity in future years could generate a parallel increase in obesity-related depression. According to the DSM-IV, an episode of major depressive disorder can be classified clinically as depression with melancholic features and depression with atypical features. Unlike melancholic depression characterized by a loss of appetite or weight, atypical depression and seasonal depression decrease activity and increase appetite and weight.

Epidemiologic studies have demonstrated that the incidence of cognitive impairment is higher in obese individuals than in individuals with normal body weight [4,5]. From the study of Anstey et al. risks of cognitive impairment appeared to be highest for those with underweight and obese in midlife [15]. Increasing evidence suggests that obesity is associated with impairment of certain cognitive functions, such as executive function, attention, visuospatial skills, and memory [4,16].

The link between such mental disorder and obesity is likely to be bidirectional: obesity can lead to mental disorder and, in turn, mental disorder can be an obstacle to treatments of obesity and attaining long-term weight-loss goals, thereby contributing to weight gain [6].

## Recent Perspective on Obesity

As described above, mental function and obesity have tight

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relationship; however, the mechanism is almost unknown, yet. Brain inflammation and imbalance of neuronal plasticity caused by dysregulation of metabolic signals are candidates which damage neurons and result in mental disorder associated with obesity according to the results of animal and human studies [17-19].

## Obesity and Brain Inflammation

Adiposity is thought to have a direct effect on neuronal degradation [5]. Microglia, macrophage-like cells of the central nervous system that are activated by pro-inflammatory signals causing local production of specific interleukins and cytokines, play a pivotal role in brain inflammation [20]. Experimental studies in animals have confirmed neurologic vulnerability to obesity and a high-fat diet and further demonstrated that diet-induced metabolic dysfunction increased brain inflammation, reactive gliosis, and vulnerability to injury, especially in the hypothalamus [21,22]. Recent studies with animals and humans have shown that other brain structures, such as the hippocampus and orbitofrontal cortex, are also affected [20,23,24]. Anti-inflammatory agent, regular treadmill running and calorie restriction were reported to be effective for improvement of these inflammatory changes in mice [22,25,26].

## Obesity and Imbalance of Neuronal Plasticity Modulated by Metabolic Signals

To explain mutual relationship between obesity and mental function, the focus of research is on imbalance of neural plasticity caused by dysregulation of metabolic signal. Leptin, adipocyte-derived hormone, insulin, secreted from pancreas  $\beta$ -cells, ghrelin, a stomach-derived hormone and glucagon-like peptide (GLP)-1, secreted from the L cells of intestinal tract, turned out to be main players as metabolic signals linking between obesity and imbalance of neural plasticity. Leptin is reported to induce an antidepressant-like activity in the hippocampus, which is considered to be an important region for regulation of the depressive state in rodents [27,28]. We previously demonstrated that development of depression associated with obesity might be due in part to impaired leptin activity in the hippocampus [28]. Given the high comorbidity of metabolic disorders, such as diabetes and obesity, with depression, several lines of evidence suggest that insulin signaling in the brain is also an important regulator in depression related to obesity. Clinical investigations show the relationship between insulin resistance and depression, but the underlying mechanisms are still unclear [29]. Ghrelin also play a potential role in defense against the consequences of stress, including stress-induced depression and anxiety and prevent their manifestation in experimental animals [30]. There might be different subtypes of depression which are better treated with leptin, insulin or ghrelin. Postulated mechanisms which obesity results in cognitive impairment are the effects of hyperglycemia, hyperinsulinemia, poor sleep with obstructive sleep apnea, and vascular damage to the central nervous system [31,32]. In animal studies, chronic dietary fat intake, especially saturated fatty acid intake, contributes to deficits in hippocampus- and amygdala-dependent learning and memory in rodents with diet-induced obesity by changes in neuronal plasticity [33,34]. Several lines of electrophysiological and behavioral evidence demonstrate that leptin and insulin enhance hippocampal synaptic plasticity and improve learning and memory [32,35]. Therefore, it is likely that impairment of the actions of leptin or insulin might be attributable to cognitive deficits in obesity and diabetes mellitus [36,37]. Through both direct and indirect actions, leptin and insulin diminish perception of food reward-the palatability of food-while enhancing the response to satiety signals generated during food consumption that inhibit feeding

and lead to meal termination. By contrast, ghrelin enhances hedonic and incentive responses to food-related cues [38]. Orexin signaling is required in these ghrelin's action on food reward [38]. Ghrelin is also reported to mediate stress-induced food-reward behavior in mice [39]. GLP-1 is turned to be an important player in reward from animal studies. Recently, GLP-1 analogue liraglutide in addition to an energy-deficit diet and exercise program, led to a sustained, clinically relevant, dose-dependent weight loss in human [40]. This successful result might arise, at least in part, from improvement of dysregulation of reward circuit. In obesity, dysregulation of these metabolic signals might change neural plasticity in many brain regions resulting in behavioral change. Literature reviews and numerous empirical studies which described significant improvements in psychosocial functioning after bariatric surgery support these ideas [41].

## Remarks

Mental aspect of obesity has been catching light very recently. To assess and treat mental aspect of obesity was only vaguely recognized so far. Being overweight and obesity might be a phenotype of over-adaptation for coping with continuous dynamic metabolic changes to protect brain. Such over-adaptation via dysregulation of brain inflammation and imbalance of neural plasticity might result in mental disorders. Clinical studies suggest that mental disorders associated with obesity can be reversible by body weight loss therapy [42-44]. We need clinical prospective data on how body weight, adiposity and muscle mass correlate with brain inflammation and imbalance of neural plasticity, eventually mental functions.

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