A quick look at obesity; the enemy within

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ABSTRACT
Obesity with an increasing prevalence rate worldwide is correlated with multiple comorbidities. Unfortunately, the currently available therapies such as the pharmacotherapy, bariatric surgery or gene-transfer technology are associated with a number of disadvantages including undesirable side effects, poor compliance or transient effectiveness. Therefore, modifications of the lifestyle factors might be of great importance. Recently, neurotrophic factors and their metabotrophic potential in targeted pharmacology against obesity has been the focus of intense research. Meanwhile, because of the complexity and multi-factorial nature of obesity, it will still remain as a challenging medical problem.

Keywords: Obesity, Brain, Chemical contributors, Therapeutic approaches.

Introduction
Obesity or excessive body fat is the result of a chronic surplus in energy intake in relation to the energy requirements. It affects public health and is associated with an increasing prevalence rate worldwide as well as multiple comorbidities including diabetes mellitus, arterial hypertension and cardiovascular diseases (1, 2). From a thermodynamic viewpoint, obesity occurs when the homeostatic controls of eating are disturbed. In fact, the control of eating behavior implies a complex multimodal communication between various organs of the body and the central nervous system (CNS) that is mediated by neural and blood-borne signals (3). Because of the complexity and multi-factorial nature of obesity, understanding the basis of how the balance between energy intake and expenditure is regulated, has been a longstanding challenge in fundamental biology.

Obesity and the brain
Studies of feeding behavior in animals and humans have encouraged the neuroscientists to search for pathways, genes, or mediators in the brain that are involved in the control of food intake and body weight. The role of the hypothalamus, as a brain region fundamentally involved in the pathogenesis of obesity, has been shown many years ago (4). Findings from the lesion study and functional brain imaging have pointed to the ventromedial hypothalamus as the ‘satiety center’ and considered the lateral hypothalamic area as the ‘hunger center’. In recent years, identification of the orexigenic and neuropeptidergic systems has revolutionized our understanding of the hypothalamic control of food intake (5-7). Novel anorexigenic factors have also been identified such as cocaine- and amphetamine-regulated transcript peptide (8, 9).
In addition, several peripheral signals are recognized in the regulation of food intake with a recent focus on ghrelin and peptide YY. Ghrelin, a polypeptide discovered in 1999, is released principally from the stomach and the upper small intestine (10, 11). Ghrelin is secreted just before an expected meal and strongly promotes food intake leading to obesity (12, 13).

Peptide YY is produced in the digestive tract in response to a meal and opposes the action of neuropeptide Y (14, 15). Meanwhile, only the discovery of leptin in 1994 resulted to a thorough understanding of the central control of eating behavior. Leptin is the best-characterized peripheral signal which is secreted principally from the white adipose tissue. It is also synthesized in other tissues such as the placenta and hair follicle (16-18). Leptin is the primary homeostatic signal for the CNS that informs the brain of the amount of body fat. It modulates neuronal activity in several regions of CNS primarily in the hypothalamus which integrate responses to meal consumption by enhancing the sensitivity to blood-borne and neurally mediated satiety signals including cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), peptide YY 3-36 (PYY 3-36). This cytokine-like hormone interacts with several orexigenic and anorexigenic pathways in the hypothalamus. The neuropeptide Y, melanin-concentrating hormone, orexin A, agouti-related peptide and cannabinoid systems have each been reported to be inhibited by leptin (19-23). The anorexigenic systems of pro-opiomelanocortin/melanocortin, cocaine- and amphetamine-regulated transcript and corticotrophin-releasing hormone are up-regulated by leptin (24, 25). In the last decade, growing interest has been attracted towards a group of neuromodulatory lipids and their receptors, called the endocannabinoid system. This ubiquitous signaling system is involved in a variety of physiological processes including the regulation of feeding behavior (26, 27). Emerging data suggests that the cannabinoid receptor agonist delta-9-tetrahydrocannabinol (THC) acts via the cannabinoid CB1 receptors on hypothalamic nuclei and directly increases appetite. It is thought that hypothalamic neurons tonically produce endocannabinoids to regulate hunger (28). The amount of endocannabinoids produced is inversely correlated with the amount of leptin in the blood. For example, mice without leptin not only become massively obese but have higher-than-normal levels of hypothalamic endocannabinoids.

Similarly, when these mice are treated with an endocannabinoid antagonist such as rimonabant, food intake is reduced. When the CB1 receptor is knocked out in mice, these animals tend to be leaner and less hungry than wild-type mice (29). Meanwhile, there are reports indicating that endocannabinoids affect feeding behavior not only at the hypothalamic level, but also at the level of taste cells in taste buds where the endocannabinoids potentiate the strength of neural signaling for sweet taste (30-33). Interestingly, neuroscientists have found that fatty food affects the pleasure centers of the brain. In this context, eating becomes compulsive for addicted individuals regardless of the negative impacts on health or social compliance (34). Latest research findings show that after extended periods of excessive eating, functional connections in the brain are altered (35). In rats, high-fat diet affects the pleasure centers of the brain and when rats are offered healthy food after weeks of junk food, they are less likely to take it, indicating that established eating habits are usually difficult to change quickly (36).

Connecting other chemicals and genetic contributors to obesity

Besides the aforementioned hormones or chemical signals, the ingesting foreign molecules including some drugs may result to obesity. While
most drugs are not truly toxins, some of them might have toxic effects and cause weight gain. For instance, psychotropic drugs have been shown to promote weight gain. In this sense, monoamine oxidase (MAO) inhibitors, lithium, valproate, mirtazapine, clozapine, olanzapine, and some selective serotonin re-uptake inhibitors (SSRIs) such as fluoxetine, sertraline, and paroxetine have all been shown to induce obesity through multiple mechanisms (37). Other foreign chemicals including environmental toxins can also cause weight gain. Environmental toxins may interfere with metabolism, hepatic detoxification systems, central weight-control systems, circadian rhythms, stress response or thyroid function leading to obesity (38). Since detoxification is a central component in long-term effective weight management and creating a healthy metabolism (39), therefore, recognizing the role of toxins in obesity and altered function of mitochondrial and redox systems or the neuro-endocrine immune supersystem will lead to the development of effective clinical strategies against obesity.

Regarding the contribution of genetic factors to the pathogenesis of obesity, brain researchers believe that gene mutations can cause obesity. In this context, it has been shown that some people are more prone to weight gain than others due to their genetic makeup. Obesity researchers estimate that genes are responsible for 40 to 70 percent of the differences between body types (40). However, geneticists have found only rare gene mutations that contribute to the isolated cases of obesity. Therefore, further genetic studies appear necessary to improve our understanding of the mechanisms linking the genetic factors to obesity.

Therapeutic approaches to obesity: the current status and future perspectives

Currently available therapies employed against obesity have ranged from modifications of lifestyle factors including the nutrition and physical activity to pharmacotherapy, bariatric surgery and gene-transfer technology (41, 42). However, these treatments are accompanied by some disadvantages including poor compliance, transient effectiveness or undesirable side effects. In particular, drug treatment for obesity is burdened with frequent and severe adverse effects including the cardiovascular diseases (43). In general, there are no effective treatments applicable to the large majority of obese/overweight people. Hence, therapeutic solutions that target the behavioral, chemical or genetic components of the disease are all in development. For example, an appetite-reducing drug that is currently under clinical investigation, activates natural hunger-dampening chemicals and at the same time, blocks the activities of hunger-stimulating chemicals. In general, the current medical attitude is to treat the complications of obesity (e.g. dyslipidemia, hypertension, diabetes, and cardiovascular diseases). Sibutramine, orlistat and rimonabant are currently licensed anti-obesity drugs. Sibutramine is a centrally acting serotonin/noradrenaline reuptake inhibitor that mainly increases satiety. At the level of brown adipose tissue, sibutramine facilitates energy expenditure by increasing thermogenesis. This drug not only reduces body weight and waist circumference, but also reduces triglycerides and uric acid. In addition, sibutramine is able to increase HDL cholesterol. Meanwhile, sibutramine has conflicting effects on blood pressure and elevates pulse rate, therefore, it is not recommended in patients with uncontrolled hypertension or a history of cardiovascular/cerebrovascular disease (44). Another drug, orlistat, is a pancreatic lipase inhibitor that reduces fat absorption by partially blocking the hydrolysis of dietary triglycerides. Orlistat significantly reduces waist circumference, blood pressure, total and LDL cholesterol, but has no effect on HDL and triglycerides. This drug also reduces the incidence of diabetes in subjects with impaired glucose tolerance. The major adverse effects with orlistat are mainly gastrointestinal (fatty and oily
stool, fecal urgency, oily spotting, fecal incontinence) and its consumption should be avoided in patients with chronic malabsorption and cholestasis (45). Rimonabant, the selective antagonist of cannabinoid type 1 receptor, by inhibiting the overactivation of the endocannabinoid system produces anorectic stimuli. In addition, rimonabant is able to affect the peripheral organs including liver, adipose tissue and skeletal muscles that are involved in the metabolic processes. Chronic treatment with rimonabant results to the elevation of HDL cholesterol and reduction of triglycerides. Meanwhile, it is not recommended in patients with a history of depressive disorders or suicidal attempts and is contraindicated in patients with ongoing major depression or antidepressant treatment (46).

Finally, we briefly look at the neurotrophic factors that have recently attracted growing attention. Substantial evidences indicate that nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), in addition to their involvement in neuronal survival, mediate multiple biological phenomena ranging from immunotrophic to psychotropic effects (47-49). These two factors are involved in the maintenance of cardiometabolic homeostasis including glucose and lipid metabolism as well as energy balance, cardioprotection, and wound healing. Recent findings demonstrate that the circulating and/or tissue levels of both NGF and BDNF are altered in cardiometabolic diseases such as atherosclerosis, obesity, type 2 diabetes and metabolic syndrome. Therefore, these multifunctional factors appear promising for the treatment of obesity or its related disorders.

**Concluding remarks**

Obesity is a health problem in which excess body fat has accumulated to the extent that it may have an adverse effect on health, leading to reduced life expectancy and/or increased health problems. Currently available therapies against obesity are associated with a number of disadvantages including poor compliance, transient effectiveness or undesirable side effects. In general, dieting and physical exercise are the mainstays of treatment for obesity. Moreover, it is important to improve diet quality by reducing the consumption of energy-dense foods such as those high in fat and sugars, and by increasing the intake of dietary fiber. Recently, neurotrophic factors and their metabotropic potential in targeted pharmacology against obesity or its related diseases has been the focus of intense research. Multiple potential of these molecules represents them as promising novel therapeutic agents against obesity and metabolic-related disorders.

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