

New Research Advances in Obesity: Relevant to Neurologic Disorders

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Obesity is a chronic medical condition. In the United States, over two-thirds of adults are overweight, and one in three Americans is obese [1]. Obesity may cause a plethora of medical conditions such as diabetes, hypertension, heart disease, depression, dementia, degenerative osteoarthritis, certain types of cancer [2], and other chronic illnesses. In clinical neurology practice, disorders related to or exacerbated by obesity include stroke [2], headache [3], and nerve damage such as carpal tunnel syndrome [4], meralgia paresthetica [5], idiopathic intracranial hypertension [6], and multiple sclerosis [7].

The two most common indexes in classifying obesity are: body mass index (BMI) and waist-to-hip ratio. BMI, a ratio of body weight in kilograms divided by height in meters squared, is widely used for estimating body fat for most adults between 19 to 70 years of age, and correlates well with total body fat content in adults, despite that it does not distinguish excess fat from muscle builders and pregnant women. An adult who has a BMI of 25-29.9 is considered overweight and over 30 obese. BMI of 35-40 is classified as severe obesity, 40-44.9 morbid obesity, and BMI greater than 45 is super obesity. Considering ethnic factors, some nations have redefined obesity as BMI greater than 25 in Japan [8] and greater than 28 in China [9].

The measurement of waist-to-hip ratio (in inches) takes into account not only how much fat a person has but also where the fat is deposited. It is obtained by measuring the waist at its narrowest point and the hips at the widest point. The pattern of body fat distribution differs in men and women. Women usually deposit fat in their hips and buttocks, displaying a “pear” shape, while men deposit fat in abdomen, making an “apple” appearance. Waist-to-hip ratios of greater than 0.8 in women and more than 1.0 in men are “apples”. Apple-shaped individuals are more likely to suffer from medical problems related to obesity.

Obesity has an adverse effect on health, leading to reduced life expectancy. On average, obesity reduces life expectancy by six to seven years [2,10], A BMI of 30-35 reduces life expectancy by two to four years, while severe obesity (BMI > 40) reduces life expectancy by 10 years [11].

Obesity has been implicated in the development of several neurological disorders as a modifiable risk factor. It may directly and/or indirectly cause or exacerbate cardiovascular diseases, including stroke [2]. Stroke accounts for roughly one out of every 18 deaths and is the third leading cause of death in the United States. Approximately 795,000 Americans experience a stroke every year, which approximates to one stroke every 40 seconds [12]. It is well known that obesity causes insulin resistance leading to development of type II diabetes mellitus (DM) [13]. It is estimated that approximately 8.3% of all ages of Americans are affected by DM [14] in which approximately half would suffer from neuropathy [15]. Certain types of neuropathies may be directly caused by obesity, such as carpal tunnel syndrome [4] and meralgia paresthetica [5].

Chronic pain syndromes, including headaches from idiopathic intracranial hypertension, or pseudotumor cerebri, are frequently seen in obese individuals. The severity and frequency of migraines

was well correlated with the degree of obesity [1,3,16]. On the other hand, weight loss may help to diminish migraines in obese individuals, for example, bariatric surgery, which reduces body weight, significantly reduces the frequency of migraine headaches in obese 17,18a and 18b cognitive functions [19,20]. Moreover, obesity may increase the risk of developing CNS demyelination, such as multiple sclerosis (MS), in young adults. Obesity at age 18 (BMI>30 kg/m²) is associated with a greater than twofold increased risk of MS (p=0.001), implying that prevention of adolescent obesity may contribute to reduced MS risk [7].

Currently, an oversimplified concept relative to the development of obesity is that it is a combination of excessive food intake and inadequate physical activity [21]. It is generally agreed that obesity results from interplay between genetic and multi-environmental factors. Genetics affect hormones that may be involved in fat regulation. Obesity has a familial tendency. An individual is more likely to become obese if one or both parents are obese. Environmental factors including diet habits such as overeating, frequent, and psychological eating [22,23], sedentary life style [24,25], diseases, and medications may accelerate the development of obesity. However, medical treatment for obesity is usually disappointing and short-lasting.

Over the last several decades progress made in obesity research has provided a wealth of information. Genetic approach provides a powerful tool in solving some of the puzzles. Polymorphisms in various genes controlling appetite and metabolism predisposed to obesity when sufficient food energy is present [26]. People with two copies of the FTO gene (fat mass and obesity associated gene) has been found to have greater risk of obesity compared to those without the risk allele [27]. Human leptin, a hormone comprising of 167 amino acids, is produced in fat cells and also in the placenta. It plays a key role in regulating energy intake and energy expenditure, including appetite and metabolism. The human leptin gene is located on chromosome 7 [28]. Leptin controls body weight by signaling the brain to eat less when body fat stores are too high. If an inadequate amount of leptin is produced or leptin cannot signal the brain to eat less, obesity occurs.

Since the discovery of leptin, ghrelin, insulin, orexin, PYY 3-36, neuropeptide Y, adiponectin, and many other signaling molecules have been added to the list of neurohormones that are implicated in energy metabolism. Of those, ghrelin is of particular interest because leptin

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and ghrelin are considered to be complementary in their influence on appetite.

Ghrelin is a 28 amino acid peptide of hunger-stimulating hormone. It is produced primarily in the fundus of the human stomach and epsilon cells of the pancreas [29]. Ghrelin levels increase before and decrease after meals [29]. Ghrelin counteracts the effect of leptin which mediates long-term appetitive controls. Although administration of leptin may be effective in a small subset of obese individuals who are leptin deficient, most obese individuals are leptin resistant and have been found to have high levels of leptin [30]. This resistance is thought to explain in part why administration of leptin has not been effective in suppressing appetite in most obese people [31].

A newly discovered myokine, or muscle synthesized hormone, named irisin (after the Greek goddess messenger Iris), may shed additional light on the nature of signaling molecules that are involved in the development and/or progression of obesity. Boström and colleagues demonstrated that over expression of transcriptional co-activator PPAR-c co-activator-1 a (PGC1-a) in mouse muscle, stimulates the expression of FNDC5, a membrane protein that is cleaved and secreted as irisin. It comprises 112 amino acids and acts on white adipose cells, where the fat is stored, to stimulate UCP1 expression and a broad program of brown-fat-like cells development in vitro and in vivo [32]. The brown fat cells are rich in mitochondria and capable of producing energy and heat. Importantly, release of irisin could be induced with exercise, which in turn causes an increase in energy expenditure and reduces body weight in mice with no changes in movement or food intake [32]. The findings of increased irisin level by either exogenous source such as injection or gene transfer observed in animals or endogenously produced by exercise observed in both animals and humans bear a possible therapeutic potential [32]. If proven to be effective in reducing obesity and improving glucose homeostasis in clinical trials, irisin could be used for human metabolic diseases such as obesity and DM, and its related neurological disorders. Viewed in this context, the potential impact of irisin on metabolic diseases and clinical neurology practice may be expected for years to come.

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