

Review article

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Pathophysiology and clinical characteristics of hypothalamic obesity in children and adolescents

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The hypothalamus plays a key role in the regulation of body weight by balancing the intake of food, energy expenditure, and body fat stores, as evidenced by the fact that most monogenic syndromes of morbid obesity result from mutations in genes expressed in the hypothalamus. Hypothalamic obesity is a result of impairment in the hypothalamic regulatory centers of body weight and energy expenditure, and is caused by structural damage to the hypothalamus, radiotherapy, Prader-Willi syndrome, and mutations in the *LEP*, *LEPR*, *POMC*, *MC4R* and *CART* genes. The pathophysiology includes loss of sensitivity to afferent peripheral humoral signals, such as leptin, dysregulated insulin secretion, and impaired activity of the sympathetic nervous system. Dysregulation of 11 β -hydroxysteroid dehydrogenase 1 activity and melatonin may also have a role in the development of hypothalamic obesity. Intervention of this complex entity requires simultaneous targeting of several mechanisms that are deranged in patients with hypothalamic obesity. Despite a great deal of theoretical understanding, effective treatment for hypothalamic obesity has not yet been developed. Therefore, understanding the mechanisms that control food intake and energy homeostasis and pathophysiology of hypothalamic obesity can be the cornerstone of the development of new treatments options. Early identification of patients at-risk can relieve the severity of weight gain by the provision of dietary and behavioral modification, and antiobesity medication. This review summarizes recent advances of the pathophysiology, endocrine characteristics, and treatment strategies of hypothalamic obesity.

Keywords: Hypothalamus, Insulin, Leptin, Obesity

Introduction

The hypothalamus plays an important role in the regulation of body weight by balancing the intake of food, energy expenditure, and body fat stores. Hypothalamic obesity is thought to result from a disruption of the mechanisms that control satiety and hunger, and to be caused by structural damage to the hypothalamus, radiotherapy or the resection of a brain tumor, and genetic defects in the hypothalamus¹. Hypothalamic obesity is evident in as many as 30–50% of children undergoing surgical treatment for brain tumors, especially craniopharyngiomas and astrocytomas^{2,3}. Craniopharyngioma and its treatment which can take the form of neurosurgery or radiotherapy can cause direct damage to the ventromedial nuclei (VMN) of the hypothalamus, which are critical for appetite regulation and weight homeostasis. As the therapeutic modalities for childhood brain tumors become more effective, and a greater proportion of these patients survive until adulthood, a number of the patients have gained excessive weight. Consequently, the incidence of cardiovascular disease, metabolic syndrome, type 2 diabetes mellitus, nonalcoholic fatty liver disease (NAFLD), and sleep apnea in these patients has increased. However, the weight gain is often intractable, and not responsive to diet or exercise therapy⁴. Recent studies have shown that the consumption of dietary fats induces the apoptosis of neurons and a reduction of synaptic inputs in the arcuate nucleus (ARC)

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and lateral hypothalamus (LH) in rodents⁵. Therefore, further investigation into the pathophysiology of hypothalamic obesity could enhance our understanding of the mechanisms of weight regulation and obesity and lead to the development of new treatment options. This review summarizes recent advances in the pathophysiology, endocrine characteristics, and treatment strategies of hypothalamic obesity in children and adolescents.

Hypothalamic control of appetite and energy regulation

The hypothalamus is known to be the master gland of weight equilibrium. It interprets afferent signals from peripheral tissues, and sends efferent signals to expend or store energy. The main hypothalamic areas involved in energy regulation are the medial hypothalamus which consists of the VMN, ARC, and paraventricular nucleus (PVN), and the LH⁶. The ARC contains two groups of neurons. The first group of ARC neurons generates orexigenic peptides, such as agouti-related protein and neuropeptide Y (NPY). The second group secretes anorexigenic peptides like proopiomelanocortin (POMC), and cocaine- and amphetamine-related transcript (CART). POMC neurons are a precursor of the anorectic peptide α -melanocyte-stimulating hormone (α -MSH). The α -MSH acts at the melanocortin 4 receptor (MC4R) and reduces appetite and food intake⁷. The PVN expresses melanocortin receptors 3 and 4 and NPY receptors. It also secretes neuropeptides such as corticotropin-releasing hormone, oxytocin, and vasopressin that have an anorexigenic action⁸. Afferent signals, including leptin from adipose tissue, insulin from the pancreas, and ghrelin and peptide YY from the gastrointestinal tract affect the anorexigenic center of the hypothalamus. Efferent signals from the PVN and LH in turn stimulate the sympathetic nervous system (SNS) or the vagus nerve through the autonomic nervous system. Efferent signals from these hypothalamic nuclei also include growth hormone-releasing hormone, somatostatin, and thyrotropin-releasing hormone, which control adipose tissue metabolism and the metabolic rate by regulating the secretion of pituitary hormones, such as adrenocorticotropic hormone, GH, and thyroid stimulating hormone^{6,9}.

Additionally, dysregulation of the SNS, insulin hypersecretion through vagus nerve stimulation, and hypercortisolemia by dysregulation of 11 β -hydroxysteroid dehydrogenase 1 (11 β -HSD1) could influence the development of hypothalamic obesity.

Etiology and pathophysiology of hypothalamic obesity

Hypothalamic obesity occurs as a consequence of structural damage to the hypothalamus, i.e., brain tumors, inflammation, trauma, neurosurgery, radiation therapy, and cerebral aneurysm (Table 1). Excessive weight gain can develop in one-third of patients who have undergone a resection of space-occupying lesions in the hypothalamic-pituitary region, such as pituitary

adenoma, germinoma, craniopharyngioma, and astrocytoma. Several risk factors have been identified as predisposing survivors of childhood brain tumors to the development of obesity: hypothalamic location, high radiation dose, extent of surgery, and tumor histology such as craniopharyngioma and astrocytoma^{10,11}. The presence of other endocrine dysfunctions, especially GH deficiency, also aggravates weight gain¹².

Several monogenic obesity syndromes involve genetic defects in the weight-regulating hypothalamic pathways, and even simple obesity can be caused by polymorphisms in these genes¹³. Understanding of the accompanying hormonal changes in these syndromes helps define the pathophysiology of hypothalamic obesity. Bardet-Biedl syndrome (BBS) is characterized by rod-cone dystrophy, postaxial polydactyly, mental retardation, hypogonadotropic hypogonadism, and renal dysfunction, and is also associated with hypothalamic obesity¹⁴. In this syndrome, 52% of patients are obese and 16% are morbidly obese¹⁴. Rapid-onset obesity with hypoventilation, hypothalamic dysfunction, and autonomic dysregulation (ROHHAD) syndrome is characterized by the remarkable feature of rapid-onset obesity, which begin between two and four years of age, and is accompanied by late-onset hypoventilation, the clinical features of Cushing disease, cortisol deficiency, GH deficiency, central hypothyroidism, hypogonadotropic hypogonadism, and hyperprolactinemia¹⁵. The pathophysiology of ROHHAD syndrome has not yet been identified, however, genetic causes are suspected because of the lack of structural damage to the hypothalamus.

Prader-Willi syndrome (PWS) accompanies hypothalamic endocrine dysfunction, which exacerbates weight gain. However, the pathophysiology of the hypothalamic dysfunction in PWS

Table 1. Structural damages leading to hypothalamic obesity¹³

Tumor
Craniopharyngioma
Pituitary macroadenoma
Glioma
Germinoma
Hamartoma
Chordoma
Ependymoma
Meningioma
Teratoma
Leukemia
Langerhans cell histiocytosis
Metastasis
Inflammatory
Sarcoidosis
Tuberculosis
Arachnoiditis
Encephalitis
Head injury
Neurosurgery
Radiation
Aneurysm

seems to be different from the other causes of hypothalamic obesity. The key finding is markedly increased ghrelin levels in the fasting and postprandial state compared to control subjects¹⁶⁻¹⁸), which contributes to hyperphagia and obesity. In addition, lower fasting and postprandial insulin levels in PWS compared to non-PWS obese subjects have been observed¹⁸). Serum leptin levels are high in the patient with PWS and show significantly positive correlations with body weight¹⁹), and leptin resistance in these patients is similar to that of patients with hypothalamic obesity caused by anatomical damage. In a recent study, a microdeletion of the noncoding HBII-85 small nuclear RNAs (snRNAs) caused clinical characteristics similar to PWS²⁰). However, the HBII-85 snRNA cluster has as-yet-unidentified targets in the brain, which affect appetite, and neuroendocrine and other brain functions that lead to PWS-associated phenotypes.

Many psychotropic drugs, including antidepressants, mood stabilizers, antipsychotic drugs, and antiepileptic drugs can lead to severe weight gain. The mechanism of weight gain is related to a complex and highly redundant network of neurotransmitters, neuromodulators, cytokines, and hormones which are involved in appetite control²¹). Some of these drugs increase peripheral insulin resistance or insulin secretion from the pancreatic β -cells²²). Clozapine and olanzapine, as well as other atypical antipsychotic medications, are associated with more weight gain than classical neuroleptics. In these drug-treated patients, hyperphagia is significantly increased²³), and hyperleptinemia and hyperinsulinemia manifest²⁴).

Clinical and endocrinological features of hypothalamic obesity

Patients with hypothalamic obesity show extreme hyperphagia, i.e., abnormal food-seeking behavior, such as foraging for food, stealing food or stealing money for food²⁵). These behaviors resemble those seen in patients with PWS or MC4R deficiencies^{26,27}). Patients with hypothalamic obesity have an increased prevalence of impaired glucose tolerance, type 2 diabetes mellitus, hypertension, sleep apnea, NAFLD, and cardiovascular risk⁴).

Many patients with craniopharyngioma with hypothalamic involvement, leptin deficiency, BBS, and PWS show reduced physical activity. The most prominent and concerning complaints in patients undergoing surgical treatment for brain tumors are persistent fatigue and lack of energy despite hormonal replacement therapy²⁸). Patients with hypothalamic obesity manifest another dysfunction of the hypothalamus, resulting in somnolence, behavioral changes, and hypopituitarism^{28,29}). Monogenic obesity in some patients is accompanied by other endocrine dysfunctions, such as hypogonadotropic hypogonadism (leptin deficiency), and GH deficiency and thyrotropin deficiency (leptin receptor deficiency). Hypogonadotropic hypogonadism and GH deficiency also occur in patients with PWS³⁰).

Hypothalamic obesity is associated with several endocrine

dysfunctions, such as hyperleptinemia, hyperinsulinemia, reduced SNS tone, dysregulation of 11 β -HSD1 and melatonin, and a decreased basal metabolic rate.

Leptin, a hormone synthesized in the fat cells, placenta, gastrointestinal tract, and possibly the brain, is primarily involved in the regulation of food intake and energy expenditure by acting as an afferent signal from the peripheral circulatory system via active transport³¹). Leptin inhibits orexigenic pathways mediated by neurons expressing the melanocortin antagonist. Leptin-deficient subjects exhibit intense hyperphagia with food-seeking behaviors³²). Homozygous mutations in the human *LEPR* gene result in early-onset morbid obesity, accompanied by hypogonadotropic hypogonadism, GH deficiency, and thyrotropin deficiency³³). In patients with simple obesity, an increase in plasma leptin levels may not be adequately translated into regulatory signals to control excessive weight gain, suggesting leptin insensitivity. Leptin levels corrected for body mass index (BMI) are higher in patients with hypothalamic obesity than in simple obesity, indicating more severe leptin resistance in hypothalamic obesity³⁴).

The primary defect in hypothalamic obesity is altered neural regulation of the β -cells resulting in insulin hypersecretion, in contrast to simple obesity where peripheral insulin resistance is the primary defect driving a compensatory β -cell response³⁴). Compared to simple obese children, hypothalamic obesity patients have a higher insulin response to glycemic loads^{34,35}). However, children with hypothalamic obesity frequently have normal fasting insulin levels³¹). Another study reported that hypothalamic obesity is associated with metabolic syndrome and cardiovascular morbidity without increased insulin sensitivity³⁶). These results suggest that hypothalamic obesity cause insulin hypersecretion without insulin resistance. Several mechanisms contribute to hyperinsulinemia, i.e., pathology in the POMC-MC4R pathway, loss of central insulin signaling, and loss of parasympathetic inhibition. Hypothalamic POMC neurons are critical for controlling homeostatic function³⁷), and subjects with MC4R deficiency have severe hyperinsulinemia due to decreased sensitivity to α -MSH²⁷). It has been postulated that hyperinsulinemia contributes to growth without GH phenomenon in hypothalamic obesity^{38,39}).

SNS is a key regulator of the metabolic rate of adipose tissue by fat mobilization and thermogenesis. Recent data has shown that hypothalamic obesity patients with craniopharyngioma have decreased urinary homovanillic acid and vanillylmandelic acid, indicating reduced sympathetic tone⁴⁰). Another study demonstrated the selective impairment of hypoglycemic counterregulatory sympathoadrenal activation in patients who had undergone surgery for craniopharyngioma, and this result supports the view that hypothalamic centers are crucial for the coordination of sympathetic counterregulatory responses during hypoglycemia⁴¹). As previously mentioned, patients with hypothalamic obesity show high leptin levels and low insulin resistance compared to patients with simple obesity, and these findings may be related to the dysregulation of the signaling pathways in the afferent and efferent arms through the SNS.

Dysregulation of the SNS in hypothalamic obesity is thought to be involved in the disruption of ARC leading to a reduction in the basal metabolic rate. Leptin has been suggested as one of the endogenous signaling molecules in the CART-mediated sympathetic neural pathway⁴²⁾.

11 β -HSD1 converts cortisone to cortisol and is expressed in several organs, such as the liver and adipose tissue. A study showed that the urinary free and conjugate cortisol/cortisone and their metabolites (11-OH/11-oxo) were significantly high in patients with hypothalamic obesity, and this ratio showed a significant correlation with the ratio of visceral fat/subcutaneous fat⁴³⁾. These results demonstrated enhanced cortisone-to-cortisol conversion in hypothalamic obesity and imply that the hypothalamus conveys a signal to the peripheral circulatory system, which modulates its 11 β -HSD1.

Melatonin, a pineal indoleamine, is secreted during the hours of darkness and influences the circadian rhythm. Since sleep regulation and circadian rhythms are partially mediated by hypothalamic structures, sleep disturbance is shown in patients with childhood craniopharyngioma⁴⁴⁾. Increased daytime sleepiness is related to decreased nocturnal melatonin levels, and nocturnal melatonin levels have been related to the degree of obesity in patients with craniopharyngioma⁴⁵⁾.

Medical and surgical treatment of hypothalamic obesity

The treatment of hypothalamic obesity requires an understanding of its pathophysiology. The conventional treatments are a calorie-restricted diet, exercise therapy, or pharmacologic treatment, but there is no effective treatment for hypothalamic obesity. Hyperphagia is difficult to control, and most attempts at behavior modification have proved unsuccessful. Pharmacotherapy focuses on alterations in the efferent pathways, such as sympathomimetics, triiodothyronine, and somatostatin analogue. Given the limited choices and poor results of pharmacotherapy, emerging data support the role of surgical treatments as effective options. There is no consensus regarding optimal weight management strategies, however, the best treatment is prevention.

Since the mechanism of hypothalamic damage decreases the activity of the SNS and reduces basal metabolic rate, sympathomimetics are a good therapeutic option. A study demonstrated that dextroamphetamine sulfate treatment following surgical resection for craniopharyngioma can achieve weight maintenance and improvements in children's activity and attention, however, their insulin levels or caloric intake did not change⁴⁶⁾. In a study of 12 patients with dextroamphetamine therapy, a stabilization or reduction in weight and improvements in daytime wakefulness and exercise tolerance were evident⁴⁷⁾, while, another study showed that treatment with ephedrine and caffeine appeared to help patients lose or maintain weight⁴⁸⁾. However, these studies only included a small number of patients. Thus, large cohort studies are needed to evaluate the overall efficacy of these treatments.

The somatostatin analog, octreotide, binds to somatostatin receptor-5 on the β -cell membrane, which restricts insulin release. In an open-label pilot study, treatment for six months with octreotide promoted weight loss or stabilization in eight patients with hypothalamic obesity, and this was accompanied by an improvement in glucose tolerance and decreased leptin levels³⁵⁾. A double-blind, placebo-controlled trial of 10 subjects showed that octreotide treatment resulted in insulin suppression, stabilization of weight and BMI, and an improvement in quality of life⁴⁹⁾.

Thyroid hormones play an important role in the regulation of energy balance, in particular, through the stimulation of the SNS. Deiodinase type II (D2), which is mainly present in the brain, brown fat, placenta, pituitary and muscle, is essential for the generation of T3 in tissue. In brown fat, D2 activity is stimulated by leptin⁵⁰⁾ and contributes to systemic T3 levels. In three patients with hypothalamic obesity, T3 supplementation promoted weight loss⁵¹⁾.

Sibutramine is a nonspecific inhibitor of the presynaptic reuptake of serotonin and norepinephrine. A double-blind, placebo-controlled trial of 21 subjects showed significant weight reduction through the administration of sibutramine⁵²⁾. However, sibutramine has been withdrawn from the market due to its adverse cardiovascular effects.

Glucagon-like peptide 1 (GLP-1) is a gut-derived incretin that stimulates insulin and suppresses glucagon secretion⁵³⁾. The U.S. Food and Drug Administration approved GLP-1 for the treatment of type 2 diabetes in adults. Exenatide, a GLP-1 homologue, resulted in a considerable reduction in body weight in a 17-year-old boy with severe hypothalamic obesity⁵⁴⁾. Another observational study sustained for as long as 51 months showed that treatment with GLP-1 analogues promoted substantial weight loss in eight of nine patients with hypothalamic obesity⁵⁵⁾. However, these were not controlled studies and the number of treated patients was both relatively small and restricted to adolescent and adult patients.

Bariatric surgery remains the most effective treatment for morbid obesity and is indicated for adult patients with significant obesity-related comorbidities. Laparoscopic adjustable gastric banding was performed on four adolescent patients with craniopharyngioma, and resulted in significant weight loss in all four patients⁵⁶⁾. In a patient with gastric bypass surgery, significant weight loss was also noted and insulin and leptin levels were normalized⁵⁷⁾.

Conclusions

Hypothalamic obesity is the result of impairment in the hypothalamic regulatory centers of body weight and energy expenditure, and is caused by structural, functional, and genetic defects of the hypothalamic nuclei, including the VMN, PVN, ARC, and LH. The pathophysiology includes a loss of sensitivity to afferent peripheral humoral signals, hyperleptinemia, hyperinsulinemia, impaired activity of the SNS, increased

11 β -HSD1 activity, and a low basal metabolic rate. The mechanisms of hypothalamic obesity that disrupt the regulation of appetite and body weight following structural damage in the hypothalamus and monogenic obesity syndrome have been investigated. Despite a great deal of theoretical understanding, an effective treatment for hypothalamic obesity has not yet been developed. To determine a successful therapeutic scheme, both an improved understanding of the underlying pathophysiology of hypothalamic obesity and multicenter trials to examine the efficacy of novel interventions are needed.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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