

Review of physiology, clinical manifestations, and management of hypothalamic obesity in humans

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Abstract Hypothalamic injury from acquired structural damage due to infiltrative disease, tumor, or their treatment aftereffects frequently results in the development of an obesity syndrome characterized by a rapid, unrelenting weight gain that may be accompanied by severe hyperphagia. Weight gain occurs from the disruption of the normal homeostatic functioning of the hypothalamic centers responsible for controlling satiety and hunger and regulating energy balance with resulting hyperphagia, autonomic imbalance, reduction of energy expenditure, and hyperinsulinemia. Curtailment of weight increase has traditionally been refractory to usual dietary and lifestyle interventions. Pharmacotherapy targeting insulin secretion and augmenting sympathetic output have been attempted to promote weight loss or attenuate weight gain. In addition, case reports suggest that bariatric surgery may be an effective treatment option for these patients. Hormonal deficits are often present, and their management may also have consequences for weight control. Hypothalamic obesity confers significant morbidity and mortality, and there is a need for greater elucidation of its risk factors and pathogenesis so that more effective interventions can be developed.

Keywords Hypothalamic obesity · Melanocortin system · Hypopituitarism · Craniopharyngioma

Introduction

As the epidemic of obesity and its associated ills have become an increasingly pressing public health concern, our understanding of the neuroendocrine physiology of energy balance has progressed substantially from early rat brain lesion experiments that first identified the hypothalamus as a major center regulating appetite and weight [1, 2]. In humans, an association between hypothalamic injury and obesity along with sexual immaturity, called the adiposogenital syndrome or Frohlich's syndrome was reported as early as 1900 [3, 4]. It is now well accepted that tumors of the hypothalamus or other causes of hypothalamic damage can lead to obesity in humans. Patients may be considered to suffer hypothalamic obesity (HO) if the following criteria are met: evidence of a pathologic process injuring the hypothalamus with obesity that develops subsequent to or in association with said injury [5, 6]. HO may also be accompanied by a range of hormonal deficiencies due to derangements in hypothalamic–pituitary function. In addition to structural damage, hypothalamic disease, or its treatment sequelae, genetic defects of the melanocortin system as well as pharmacotherapy (in particular, antipsychotic medications known to promote weight gain) that interfere with the normal workings of the hypothalamic centers of energy balance may be said to fall under the rubric of HO. For example, mutations of the melanocortin 4 receptor are considered to be the most common cause of monogenic obesity in humans [7] while animal data has linked antipsychotic drug induced weight gain to selective activation of hypothalamic AMP-kinase [8]. Prader-Willi Syndrome (PWS), a genetic obesity syndrome characterized by hyperphagia and severe obesity as well GH deficiency and hypogonadotropic hypogonadism, is associated with a reduction in the volumes of hypothalamic

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paraventricular nuclei and is thought to be related to hypothalamic dysfunction [9, 10]. For the purposes of this review, the definition of HO will be confined to obesity developing from acquired structural damage or lesions of the hypothalamus or their treatment sequelae. The physiology underlying the development of HO, its causes, associated risk factors, and clinical features, as well as potential treatment options will be discussed.

Pathophysiology

In the 1940s, investigators found that lesions to the hypothalamic ventromedial area, paraventricular nucleus (PVN), or dorsal medial hypothalamic nuclei produced hyperphagia and obesity in rats [1]. In contrast, lesions to the lateral hypothalamus (LH) induced hypophagia [11]. These findings gave rise to the dual center hypothesis of feeding with the ventromedial (VMH) and LH categorized as the satiety and hunger centers, respectively. Further investigation has demonstrated that within the VMH are glucose sensing neurons as well as receptors for multiple neuropeptides involved in regulating energy balance while the LH contains neurons expressing orexin (hypocretin), a neuropeptide thought to be involved in both arousal and feeding, and another potent orexigen, melanin concentrating hormone (MCH) [2, 12].

For many years, the critical role of the hypothalamic arcuate nucleus in energy homeostasis went unrecognized. The arcuate nucleus, in close proximity to capillaries at the base of the hypothalamus, is well situated to sense nutrient and hormonal signals of energy stores from the periphery, and is the primary site of two sets of neurons that form part of the central melanocortin system, a key regulator of energy balance [13–15]. These two neuronal populations express either proopiomelanocortin (POMC) or agouti-related protein and neuropeptide Y (AGRP/NPY). POMC is post-translationally cleaved to yield a number of peptide products, including adrenocorticotropin (ACTH), critical for regulating adrenocortical function, and α -melanocyte stimulating hormone (α -MSH). α -MSH acts as an agonist at the central melanocortin receptors MC3/4-R to inhibit feeding and stimulate energy expenditure (EE) while AGRP is a MC3/4-R antagonist with orexigenic effects. NPY also stimulates feeding and reduces EE. In the arcuate nucleus POMC and AGRP/NPY neurons express receptors for a number of peripheral hormones, including leptin and insulin. Both leptin and insulin stimulate arcuate expression of POMC and suppress AGRP/NPY expression. Disruption of responses to leptin and insulin from hypothalamic damage has been proposed as a possible mechanism contributing to hypothalamic obesity [16]. Several gastrointestinal hormones also affect

POMC and AGRP/NPY neuronal activity [17, 18]. For example, the appetite stimulating gut hormone ghrelin increases the firing activity of NPY and reduces POMC activity. Furthermore, arcuate POMC and AGRP/NPY neurons project fiber tracts to other hypothalamic regions, including the PVN and LH, as well as other brain areas to affect energy homeostasis. Thus, the hypothalamic melanocortin system is a key nodal point that integrates a number of neural and hormonal inputs to mediate changes in feeding and EE. Perturbations of this complex neuro-metabolic circuitry from hypothalamic damage, therefore, have the potential to result in hyperphagia and/or impaired EE with consequent obesity.

The hyperghrelinemia observed in Prader-Willi Syndrome (PWS) [19–23] has prompted investigation into whether elevated ghrelin levels are also present in HO due to acquired structural damage. Goldstone et al. [24] found that fasting plasma ghrelin in patients with HO due to craniopharyngioma was significantly lower than that of patients with PWS and did not differ from levels found in control patients with common obesity. Post-prandial area under the curve (AUC) ghrelin was similar between patients with HO and common obesity in this study, as well [24]. Likewise, Kanumakala et al. [25] also found no difference in fasting total ghrelin levels between patients with HO and controls with common diet induced obesity. Moreover, Daousi et al. [26] documented significantly lower fasting plasma ghrelin as well as lower AUC post-prandial ghrelin response among patients with HO compared to healthy controls matched for body mass index (BMI) and percent adiposity. Thus, data supporting a role for hyperghrelinemia in the pathogenesis of HO is lacking.

The autonomic hypothesis and hyperinsulinism

Investigators observed that rodents with VMH lesions developed hyperinsulinemia even in the absence of hyperphagia and prior to the onset of obesity [27–29]. Moreover, obesity developed in the VMH lesioned rat even when hyperphagia was prevented with food restriction suggesting that defects in energy partitioning and expenditure play some causative role in HO [30, 31]. Significantly higher fasting insulin levels among patients with HO compared to individuals with common diet induced obesity have also been documented [5]. These observations led Bray and others to postulate that VMH lesions lead to autonomic imbalance from disinhibited/increased vagal tone with hyperinsulinemia as the result of overactive vagal transmission, and that these events are major contributors to the pathogenesis of HO [5, 32–34]. Supporting these theories, studies showed that pancreatic vagotomy prevented the exaggerated secretion of

glucose-stimulated insulin in VMH lesioned rats [35–38]. Bray et al. [32] also demonstrated that rats with lesions of the VMH exhibited signs of decreased sympathetic nervous system tone as well as increased levels of glucose-stimulated insulin that were attenuated by epinephrine infusion and completely blocked by administration of both epinephrine and atropine.

There is evidence to suggest that impaired sympathetic tone and reduced physical activity play a role in the pathogenesis of HO in humans. Harz et al. [39] studied patients with HO from craniopharyngioma and found that while their caloric intake (determined by a validated food diary) did not exceed that of control patients with common obesity, their movement activity, assessed by accelerometry, was reduced both in the ambulatory setting and in a clinically monitored weight loss environment. Two studies have shown that patients with a history of hypothalamic craniopharyngioma resection have an impaired counter regulatory response to hypoglycemia with significantly lower levels of plasma epinephrine [40, 41]. Similarly, a patient with hypothalamic sarcoidosis was found to have markedly reduced epinephrine and norepinephrine responses to hypoglycemia [42]. Lower 24 h urine epinephrine excretion has also been documented in pediatric patients with craniopharyngioma compared to healthy controls, although this study did not detect any correlation with hypothalamic involvement of the tumor [41]. However, Roth et al. [43] found that craniopharyngioma patients whose tumor involved the hypothalamus had higher BMI values and significantly lower urinary catecholamine metabolites [homovanillic acid (HVA) and vanillylmandelic acid (VMA)] as well as lower activity scores than those without hypothalamic involvement. Moreover, in this study, patients with the most severe obesity possessed the lowest urine HVA and VMA levels [43]. These findings have prompted the use of vagotomy [44], suppression of insulin secretion [45, 46], and agents that may enhance EE through increased sympathetic output [47–49], as potential treatment options for human HO.

Causes of and associated risk factors for hypothalamic obesity

Among the causes of HO (Table 1), perhaps the most extensively documented has been that of craniopharyngioma (either from the tumor itself or as treatment sequela) in children and young adults. The frequency of HO from craniopharyngioma has been reported to be as high as 70%, depending on the case series, and up to 57% among childhood cancer survivors treated with cranial radiation [50–52]. Craniopharyngiomas are dysontogenetic tumors arising from remnants of Rathke's pouch and account for

Table 1 Causes of hypothalamic obesity

Craniopharyngioma	Sarcoidosis
Pituitary macroadenoma	Tuberculosis
Glioma	Arachnoiditis
Meningioma	Langerhans cell histiocytosis X
Teratoma	Encephalitis
Germ cell tumor	Hypodipsia-hypernatremia syndrome
Metastasis	Hamartoma
Leukemia	Aneurysm
Chordoma	Subthalamic implants
Surgery/radiation	
Head trauma	

approximately 10% of all pediatric intracranial tumors [53]. After tumor resection, over 50% of patients with craniopharyngioma are obese, and nearly half of these patients experience severe hyperphagia [54, 55]. Tumor location, particularly hypothalamic involvement is the major risk factor for the development of obesity in these patients [54–56]. One series showed that extension of the tumor to the hypothalamus was found in 76% of obese and 96% of severely obese patients compared to 33% of normal weight survivors [56]. Magnetic resonance imaging (MRI) studies in childhood craniopharyngioma have also demonstrated a significant relationship between post-operative obesity and the extent of hypothalamic injury delineated [57]. In addition, a German study reported that increased BMI at the time of diagnosis, the presence of hydrocephalus requiring ventriculoperitoneal (VP) shunt placement, and maternal BMI > 25 kg/m² were significant risk factors predictive of the development of severe obesity [55].

Lustig et al. [58] identified the following risk factors for the development of obesity in children surviving other brain tumor types in addition to craniopharyngioma: tumor location within the hypothalamus, younger age of diagnosis, and dose of radiation therapy. Hypothalamic tumors were associated with nearly double the rate of change in BMI compared with lateral ventricular tumors. While they did not detect any significant difference in BMI change rates over time between those who had received cranial radiation and those who had not, the dose of radiation delivered to the hypothalamus had a significant effect on the rate of BMI increase, with doses of 51 Gy being permissive [58]. This level of radiation dose remained significant in terms of its effect on the development of obesity independent of tumor location [58]. In contrast to Muller et al. [55], they did not observe a predictive effect of BMI increase with the need for VP shunt placement [58]. Nor did they find that the use of chemotherapy, the extent of surgery, or the long-term use of steroids in the management of cerebral edema or hydrocephalus was predictive of the rate of BMI increase. However, simply the

presence of any endocrinopathy at all was associated with significant escalation of BMI over time. Compared with other tumor types, craniopharyngiomas tended to exhibit a more accelerated rate of BMI elevation [58].

Fewer studies defining risk factors for the development of HO have been conducted in adults. One retrospective study examined 52 patients with a median age of 44 years when tumor within the hypothalamic region was diagnosed [59]. After a median follow-up time of 5 years, 52% of patients were obese compared to 24% at the time of diagnosis [59]. Patients with newly developed or worsened obesity were also more likely to be receiving some form of hormone replacement therapy. In this study, both desmopressin and growth hormone use were associated with new or exacerbated obesity upon follow-up [59]. In contrast to other studies [55, 57], Daousi et al. [59] did not find any correlation with VP shunt placement and greater risk of weight gain, nor did they detect any significant relationship between neuroanatomical extent of the tumor on MRI scan and subsequent weight elevation.

In addition to tumors, inflammatory lesions of the hypothalamus have also been associated with HO (Table 1). Neurosarcoidosis, diagnosed in less than 10% of patients over the course of the disease, has been identified in case reports as a cause of HO [5, 6, 60–62]. In addition, steroid use for the treatment of neurosarcoidosis may further exacerbate hyperphagia and weight gain [60].

Advances in treating Parkinson's disease have presented yet another potential etiology of HO. Significant weight gain has been observed in patients with Parkinson's disease treated with deep brain stimulation using subthalamic implants (DBS-STN) [63–66]. Patients have been reported to gain up to 20 kg of weight within the first year of implant placement [67]. Several studies have documented a reduction in EE that many consider to be the culprit for the weight gain [65–67]. However, disruption of the hypothalamic centers of energy homeostasis has not been completely ruled out as a possible contributing factor. Moreover, the lack of correlation between changes in daily EE and body weight as well as gender differences in the accumulation of fat mass versus fat free mass following DBS-STN suggest an impact on energy partitioning that is not solely attributable to decreases in EE [67].

Clinical features of hypothalamic obesity

Extreme hyperphagia has been noted as a striking feature of HO. However, obesity may develop even in the absence of hyperphagia. The degree of weight gain associated with HO can also be quite variable [6]. Generally, the pattern of weight gain in patients with HO is characterized as abrupt in onset and rapidly accelerating after hypothalamic injury,

at times unrelentingly so [5, 68]. Bray has suggested that an altered pattern of weight increase after hypothalamic insult as opposed to the actual magnitude of the weight gained is the defining feature indicative of HO [6]. Body weight may accrue quite rapidly, often at a rate of 1 kg/month or more [69]. In an analysis of 69 cases of HO, almost half gained more than 20 kg [5]. In a study of 43 children who had undergone primary resection of a craniopharyngioma, 58% developed obesity over a mean follow-up of 56 months [70]. Among those who developed obesity, a distinctive pattern of weight gain emerged, with BMI increasing rapidly over the initial 6 months followed by a period of stabilization from which there was no reduction in BMI [70]. This suggests that the early period following hypothalamic injury may be a crucial time for intervention to limit the extent of weight gain.

In this group, 88% developed DI and 86% developed panhypopituitarism [70]. Steroid replacement was provided by hydrocortisone at a dose that ranged from 6 to 10 mg/m²/day, and hence was not supraphysiologic to account for exacerbated weight gain [70]. These findings echo those of Daousi et al. [59] who demonstrated that desmopressin use and growth hormone were associated with new or increasing obesity in follow-up. Cranial endocrinopathies requiring hormonal replacement therapy are a common occurrence with HO.

Obesity that develops among craniopharyngioma patients has also been shown to have a major adverse impact on quality of life and functional capacity (accompanied by an overall reduction in survival rates) [56]. More features of the metabolic syndrome, including greater abdominal adiposity, have been documented among childhood craniopharyngioma patients compared to age-, sex-, BMI-, and pubertal stage-matched controls [71]. Moreover, an increased risk of cardio- and cerebrovascular mortality was observed in a study of 60 patients treated for craniopharyngioma compared to the general population during a median follow-up time of 12 years [72].

Other symptoms that have been described in association with HO include headache, impaired vision, increased somnolence, and behavioral disturbances, including hyperphagia and abnormal food seeking behaviors. Rage and dementia were noted to accompany the development of HO in a woman who was ultimately found to have a ventromedial hypothalamic hamartoma [73]. Disruptions in thermoregulatory function have also been reported [74].

Treatment

The usual cornerstone of obesity treatment is a program of lifestyle changes aimed at caloric restriction and increased physical activity. Though HO can at times seem

frustratingly refractory to such measures, a healthy diet and exercise are still to be encouraged. Indeed, animal studies suggest that exercise may be particularly helpful in attenuating further weight gain and potentially promoting some weight loss. A study of rats with monosodium L-glutamate (MSG) induced HO demonstrated that exercise training resulted in reduced adiposity compared to sedentary HO rats [75]. MSG obese mice subjected to swim training had less gonadal fat and a 68% increase in catecholamine content of the adrenal gland compared to their non-exercised counterparts [76]. Previously, other investigators had demonstrated that in comparison with unexercised normal controls, sedentary MSG-obese mice had low adrenal catecholamine content and reduced levels of enzymes involved in catecholamine synthesis [77]. Scomparin et al. [76] postulated that HO is associated with an imbalance in sympathoadrenal activity, which in the case of the MSG-HO mice was ameliorated by the early swim training activity.

These animal data suggest that increased exercise may help counteract the impaired sympathoadrenal activation described in humans [39–43], and raised the question of whether sympathomimetic pharmacotherapy might attenuate weight gain or even promote weight loss in these patients. Five pediatric patients who developed HO after craniopharyngioma resection were treated with dextroamphetamine for 24 months [47]. Each patient served as his or her own control and the doses of dextroamphetamine ranged from 12.5 to 20 mg per day, administered over three divided doses. Prior to initiation of dextroamphetamine, the mean weight gain was 2 ± 0.3 kg/month [47]. Patients were started on dextroamphetamine at a mean of 10.4 months post-operatively. Dextroamphetamine significantly reduced the velocity of weight gain to 0.4 ± 0.2 kg/month [47]. BMI stabilized after 1 month of dextroamphetamine and remained stable over the 24-month treatment protocol. This is in contrast to the significant rise in BMI from 21 ± 3.5 to 32 ± 2.8 that occurred in the 7–14 months prior to treatment [47]. Pre- versus post-treatment caloric intake did not differ, but a review of exercise logs revealed an increase in physical activity on dextroamphetamine. Patients did not experience any adverse effects or reactions to the medication [47]. Similar weight stabilization and even modest weight loss were also observed in a retrospective chart review of 12 pediatric patients treated with dextroamphetamine for HO [48].

Sibutramine, also a sympathomimetic whose mechanism of action is inhibition of the reuptake of serotonin, norepinephrine, and dopamine, is prescribed as an appetite suppressant in treating common obesity. Whether it may prove effective for treating HO is not clear, although anecdotal testimony suggests that it could be of benefit. A 17-year-old male with panhypopituitarism and a history of

suprasellar craniopharyngioma treated with surgical resection and radiotherapy developed extreme hyperphagia to the extent he required long-term supervision at a closed residential center [49]. His BMI was reported as 33 kg/m^2 . Several days after sibutramine therapy at a dose of 20 mg per day, the incapacitating food seeking behavior reportedly improved and his subjective hunger decreased. Unfortunately, the effect of sibutramine on body weight in this patient was not reported [49]. These results suggest that further study of the efficacy and safety of sympathomimetic pharmacotherapy in treating HO is warranted.

Another theory of perturbed autonomic system regulation contributing to HO involves disinhibited parasympathetic activity with increased vagal tone leading to insulin hypersecretion. Thus, suppression of insulin secretion with octreotide has been investigated as a potential treatment option [45, 46]. In an open label study, eight patients with HO were treated with subcutaneous octreotide (dose 15 mcg/kg/day) for 6 months [45]. Octreotide therapy resulted in a significant weight loss of 4.8 ± 1.8 kg compared to the 6.0 ± 0.7 kg weight gain during the 6 month pre-study observation period with a significant reduction in BMI by $2.0 \pm 0.7 \text{ kg/m}^2$ [45]. Recall data of caloric intake declined significantly during treatment. Hemoglobin A1c levels did not change with treatment, but a tendency toward improved glucose excursions and significantly reduced insulin secretion in response to oral glucose tolerance testing (OGTT) was observed [45]. In a 6 month randomized placebo controlled trial with octreotide in 18 patients with HO, glucose levels in response to OGTT were slightly higher in the octreotide group versus placebo, but not significantly so, while insulin responses declined significantly with octreotide use [46]. Although octreotide did not induce weight loss, there was a significant attenuation of weight gain. The placebo group gained an average of 9.1 ± 1.7 kg compared to octreotide treated patients whose average weight gain was 1.6 ± 0.6 kg [46]. Side effects of abdominal discomfort, flatulence, and loose stools as well as asymptomatic small gallstones detected by ultrasonography were noted in both studies [45, 46].

An important consideration in treating HO which is often accompanied by partial or panhypopituitarism, is optimal hormone replacement. Dexamethasone dosing in the immediate perioperative setting may not influence the development of long-term obesity [78]. However, a rationale for judicious long-term steroid replacement for adrenal insufficiency is based on the finding that HO is associated with enhanced activity of 11 β -hydroxysteroid dehydrogenase-1 (11 β -HSD-1), an enzyme expressed in human brain, liver, and adipocyte tissues and responsible for converting inactive cortisone to active cortisol [79]. The investigators of this study hypothesized that abnormal

metabolism of exogenous glucocorticoid replacement might contribute to the development of HO. Reasoning that elevated urinary cortisol to cortisone ratios reflect enhanced activity of 11 β -HSD-1, they measured the ratios of free and conjugated cortisol to cortisone as well as their metabolites in HO patients with secondary adrenal insufficiency and in control Addisonian patients [79]. They found that the ratio of 24 h urine free cortisol to cortisone among patients with HO was significantly higher than that of the control patients [79]. Though this elevated ratio did not correlate with BMI, there was a significant correlation with higher ratios and the proportion of visceral to subcutaneous fat [79]. In a separate *in vitro* study using cultured adipocytes derived from healthy humans, they found that ACTH and CRH down-regulated 11 β -HSD-1 activity providing support for the hypothesis that hypothalamic hormones play a role in regulating adipose tissue 11 β -HSD-1 and a potential mechanism for its contribution to the development/exacerbation of HO [80]. These data suggest that lower doses of steroid replacement may suffice to treat adrenal insufficiency in the setting of HO.

Thyroid hormone deficiency may also be present and require correction with levothyroxine administration. Anecdotal evidence raises the possibility that additional supplementation with triiodothyronine (T3) may be effective adjunctive treatment for HO. Fernandes et al. [81] reported three patients with HO adequately replaced with levothyroxine who then lost weight (between 4.3 and 15.2 kg) after T3 administration. None of the patients developed signs or symptoms of hyperthyroidism despite elevation of serum T3 levels above the normal range [81].

Growth hormone (GH) deficiency may also accompany HO. While growth hormone replacement can lead to reduction of fat mass and an increase in lean body mass [82], it is debatable whether similar positive effects are attained in patients with HO. One study found that four patients with craniopharyngioma experienced a significant reduction in BMI after 1 year of GH treatment [83]. On the other hand, an analysis of pediatric patients with craniopharyngioma and GH deficiency in the Pfizer International Growth Database (KIGS) found that after 3 years of GH therapy, these patients continued to have disproportionately higher weights than patients with organic GH deficiency [84]. A similar analysis of the Pfizer International Metabolic Database (KIMS) conducted among adults with craniopharyngioma compared to patients with non-functioning pituitary adenoma (NFPA) found that 2 years of GH therapy led to similar improvements in fat free mass and cholesterol levels between groups, but craniopharyngioma patients failed to exhibit a significant decrease in body fat in contrast to NFPA patients [85]. In addition, mean weight increased significantly in the group of craniopharyngioma patients, whereas it remained stable in the

NFPA group [85]. In the absence of definitive conclusions regarding the effects of GH replacement in individuals suffering from HO, it is reasonable to follow current standard practice guidelines for treating GH deficiency until future studies provide more insight.

There has not been extensive study of weight loss medications in the HO population. Available treatments that may be considered are the sympathomimetic appetite suppressants sibutramine and phentermine, and orlistat, a lipoprotein lipase inhibitor that blocks the absorption of approximately 30% of dietary fat intake. Agents that have yet to be approved for treating obesity offer promise for the future. Topiramate and zonisamide, approved for seizure disorder treatment, have been reported to induce weight loss beyond placebo in patients with common obesity [86–88]. Endocannabinoid receptor blockade may confer the advantage of exerting beneficial effects on adiposity through peripheral as well as central mechanisms [89]. Rimonabant, the first selective endocannabinoid receptor-1 blocker developed, is approved for obesity management outside the United States, and has been shown to exert metabolic benefits in terms of favorable changes in HDL cholesterol and triglyceride levels as well as insulin sensitivity beyond what might be expected from weight loss alone [90].

Bariatric surgery has also been pursued. Muller et al. [91] describe four patients with history of childhood craniopharyngioma and subsequent morbid obesity who underwent laparoscopic adjustable gastric banding. In all patients, BMI decreased or stabilized after surgery over a follow-up time of 1.5–4.5 years. Finally, there is one case report of treatment of HO with gastric bypass surgery which included a truncal anterior vagotomy to reduce vagal contribution to hyperinsulinemia [92]. After surgery, the patient experienced a marked reduction in appetite and lost 22% of initial body weight over a 2.5-year-period [92]. It is unclear if interruption in vagal tone had an overall beneficial effect since this pathway mediates multiple neurohormonal signals between the gut and brain that control satiety and gastrointestinal motility. Given the relative dearth of available safe and effective agents for treating obesity, further research is clearly needed. Therapy that targets peripheral regulators of energy balance or brain areas other than the hypothalamus involved in reward systems and the hedonic control of food intake may yield additional strategies for addressing HO.

Summary

Obesity is a frequent outcome of damage to the hypothalamus and has significant adverse effects on morbidity and mortality. The clinician must be vigilant to the increased

risk of obesity development in this population, and therapeutic interventions should be promptly initiated. HO is commonly associated with one or more hormonal deficits, and these should be optimally treated. Multiple mechanisms are likely involved in the pathogenesis of HO, and may vary depending on the extent of hypothalamic injury. Greater insight into the factors contributing to HO as well as antiobesity drugs currently under investigation offer hope for more effective therapy in the future.

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