Hypothalamic Obesity: Prologue and Promise

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Abstract

Hypothalamic obesity (HO) frequently occurs following damage to the medial hypothalamic region, encompassing the arcuate nucleus, the paraventricular nucleus, the ventromedial nucleus, the dorsomedial nucleus, and the dorsal hypothalamic area, which are critically involved in the regulation of satiety and energy balance through neural and humoral connections. HO is most commonly described in the context of craniopharyngioma and its treatment, but it can also occur following other suprasellar tumors, radiation, trauma, or a surgical insult to the hypothalamus. A constellation of loss of satiety and a reduction of the metabolic rate, thermogenesis, and physical activity as well as increased vagal tone and hyperinsulinism with insulin and leptin resistance results in rapid weight gain due to a decreased energy expenditure and increased energy storage in adipose cells. To date, no viable long-term solution for HO has been found, due either to the requirement of intact hypothalamic pathways or to significant side effects. Newer therapeutic modalities focused on the unique pathophysiology of this condition offer potential for successful treatment. In this review, we describe the etiology of HO as well as past/current treat-

ment approaches in the categories of hyperinsulinism, surgical approaches, and targeting energy expenditure/anorectic drugs. We conclude by providing an overview of the clinical trials currently underway.

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Introduction

In this review, we focus on mechanisms leading to a disturbed energy balance in patients with hypothalamic obesity (HO) in the context of craniopharyngioma (CP), postulating that these mechanisms also apply to other suprasellar brain tumors and after hypothalamic injury. Consideration is given to the physiologic rationale for various therapeutic approaches and their interactions with different pathways of energy homeostasis. This review represents published data and clinical trials through June 2018.

Etiology

The hypothalamus is critically involved in regulating homeostatic functions such as energy homeostasis. In addition, it is linked through direct synaptic connections

to appetite-regulating brain regions such as the limbic system that mediate the motivation to eat and process rewards [1]. Disruption of feeding circuits by damage to medial hypothalamic nuclei by tumor, surgery, or irradiation [2] has the potential to increase hunger by unopposed activation of orexigens from the lateral hypothalamus or by deficient responses to adiposity signals such as leptin and proopiomelanocortin in the arcuate nucleus from the medial hypothalamus.

Damage to the hypothalamus, due to either tumor invasion or treatment, results in an inability to integrate the various afferent hormone and neuropeptide signals. The mechanism for the resultant obesity is multifactorial and poorly understood. Several nuclei in the medial hypothalamus are key regulators of satiety and energy expenditure. The most common nuclei implicated in HO are the arcuate nucleus, the paraventricular nucleus, the ventromedial nucleus, the dorsomedial nucleus, and the dorsal hypothalamic area. Damage to some or all of these nuclei in the medial hypothalamus results in dysregulation of satiety and energy expenditure. Disinhibition of vagal tone due to damage to the paraventricular nucleus (sympathetic) and suprachiasmatic nucleus (SCN) (parasympathetic) subsequently alters lipogenesis and beta cell secretion of insulin. Damage to the ventromedial nucleus causes loss of satiety through the inability to coordinate afferent hormonal signals including leptin, insulin, and gut hormones like GLP-1. Additionally, disruption of autonomic function damages the biologic clock that stabilizes circadian activity.

The SCN is thought to synchronize circadian activity through the autonomic nervous system. This integration of the external and internal environments is crucial to metabolism in humans. The SCN senses sunlight and signals the paraventricular nucleus, which affects the daily rhythm of anterior pituitary hormone secretion as well as melatonin production. When the superior cervical ganglion is disinhibited by lack of light, melatonin is secreted by the pineal gland. Melatonin has been shown to affect secretion of neuropeptide Y (NPY), POMC, and other substrates such as leptin that are important in feeding regulation [1]. Studies have shown disrupted circadian rhythm, daytime somnolence, and low melatonin levels in obese CP survivors [3, 4]. A small study administering melatonin to 10 adults following CP therapy as children, showed improved physical activity and decreased daytime somnolence [5]. In our clinical practice, melatonin efficacy is limited and additional daytime stimulants (i.e. methylphenidate, modafinil, pitolisant) are often required, particularly for patients who meet criteria for

narcolepsy or hypersomnia [3]. One study revealed 40% of CP survivors had a normal pattern of melatonin secretion [4]. These patients may not respond to melatonin supplementation.

Vagal tone is paramount to β -cell insulin secretion. Excess vagal stimulation can result in increased insulin secretion both fasting and post-prandially. Insulin binding to the insulin receptor starts a cascade of metabolic signaling including increased glucose utilization in adipocytes (due to glucose transporter 4 translocation to the plasma membrane); this leads to increased glucose uptake in adipocytes and then stimulates production of leptin [6]. This chronic hyperinsulinism, with insulin resistance, causes compensatory elevation in leptin and suppression of ghrelin [7]. Damage to VMH, dorsomedial nucleus, and dorsal hypothalamic area neurons prevents the integration of afferent leptin signaling. This altered leptin signal transduction results in an inability to sense energy sufficiency or satiety. Children with HO exhibit weight gain, even in response to forced caloric restriction [8]. After the initial hyperphagia and rapid weight gain seen in the first year after hypothalamic surgery, maintenance of severe obesity is in many cases due to a lower energy expenditure and altered feeding regulation, not an increased caloric intake [9, 10]. HO is therefore a manifestation of functional leptin resistance [11]. Analyses on ghrelin and α -melanocyte-stimulating hormone in a cohort of CP patients matched to patients with similar BMI but no hypothalamic damage revealed lower ghrelin and α -melanocyte-stimulating hormone levels both at baseline and postprandially [12, 13].

Thus, suprasellar tumors (especially CP), by virtue of their hypothalamic location, have the potential to disrupt regulation of body weight and energy intake at many levels [14], resulting in a complex clinical picture of HO syndrome characterized by severe obesity associated with leptin resistance, hyperinsulinism, fatigue, hyperphagia, impaired satiety, decreased sympathetic tone, and a low energy expenditure [8–11, 15–17]. This condition is often exacerbated by altered impulse control and other behavioral changes seen with hypothalamic damage [18].

As many as 50% of patients following treatment for CP develop HO [18, 19] (Fig. 1). Other causes of hypothalamic dysfunction and damage include other suprasellar tumors, cranial irradiation, trauma, inflammation, and genetic syndromes [2, 17, 20, 21]. Factors associated with development of this condition are: the degree of invasion into the hypothalamus (especially with involvement of the mammillary bodies) [22], the presence of endocrine dysfunction at the time of diag-

Fig. 1. Typical growth pattern of a patient with HO following CP therapy, with persistent weight gain. The first plotted point is diagnosis at 4 years and 8 months. His tumor was treated with surgical excision. He had multiple hormone deficiencies at the time of

diagnosis. The tumor recurred at age 6 years and 8 months, and he had proton beam radiation. Growth hormone therapy was initiated at age 11 years and 2 months.

nosis (especially diabetes insipidus, perhaps since vasopressin is synthesized in the hypothalamus) [19], the age at diagnosis (younger children tend to have more obesity), being heavier at the time of diagnosis, a family history of obesity, and radiation over 51 Gy to the hypothalamic area [2, 18, 23, 24].

Recent data indicate that hypothalamic involvement has a major negative impact on the long-term prognosis. Sellar masses with hypothalamic involvement are associated with a lower overall survival and higher BMI at diagnosis and follow-up, compared to sellar masses without hypothalamic involvement [25]. Despite excellent overall survival rates, CP survivors have a 5-times-greater overall mortality rate and a 3-times-greater cardiovascular mortality rate than the general population [26]. Survivors who develop obesity have greater morbidity and mortality than normal-weight survivors [23]. While many patients report hyperphagia, recent studies have also reported an overall decrease in energy intake in patients with HO compared to controls [9, 10]. It is possible that a hyperphagic phase of rapid weight gain soon after surgery is followed by a long-term condition of maintenance of a high body weight status characterized by a low energy expenditure, which could explain the difficulties in reducing body weight. The reduction in energy intake is offset by a greater relative decrease in basal metabolic rate and physical activity-related energy expenditure in HO patients. In addition, unsuccessful weight loss through caloric restric-

tion and exercise is believed to be due in part to the marked decline in the resting energy expenditure from the perceived “starvation response” of increased vagal tone and decreased leptin sensitivity. Even in those patients who are motivated to reduce their energy intake and increase their activity, dietary modifications are only sporadically beneficial [27]. This may be related to other factors, such as a low energy expenditure, the home environment, and behavioral problems. We still recommend that diet and exercise be the first step and cornerstone of obesity intervention; medications become necessary when there is no response to these lifestyle modifications.

Treatment

Most efforts to treat HO have disappointing long-term success rates, as previous drug intervention studies have been small and limited by significant side effects or they have shown only moderate effects, and, as noted above, caloric restriction and exercise generally have not been successful approaches [28]. All treatment efforts have focused on bypassing the damaged hypothalamic circuits. In the absence of clinical guidelines on treatment of HO, an objective here is to provide an overview of past therapies as well as current clinical studies and advances. We have elected to organize the past studies by category of major physiologic effect.

Hyperinsulinism

As the change from using adiposogenital syndrome to the more modern concept of HO emerged in the 1970s, so did evidence for insulin hypersecretion during oral glucose tolerance testing [29]. VMH damage not only prevents integration of leptin signaling but also causes increased vagal tone. Addressing hyperinsulinism has been proposed as a therapy for HO. The most basic way to address this is through carbohydrate reduction. Formal studies have used medications to directly alter insulin secretion or sensitivity. Finally, surgical vagotomy has been proposed and studied as a mechanism to alter insulin secretion; this is described in Surgical Approaches.

Carbohydrate Restriction

Lundbaek and Stevenson [30] studied the effects of a high-fat diet in rats with HO in 1947. Since then, there have been few scattered case studies [27] showing the benefits of protein-sparing modified fasting or limitation of carbohydrates in individuals suffering from HO. Buoyed by these reports, some centers encourage low-carbohydrate diets for the treatment of HO with varying degrees of anecdotal success, especially at a level of 50 g of carbohydrates per day.

Octreotide

Octreotide is a long-acting somatostatin analog that binds to somatostatin receptor-5 on the β -cell membrane. This binding affects the opening of the calcium channel, resulting in a blunted first-phase insulin response. Octreotide was first used in a pilot study to address the hyperinsulinemia seen in HO. In that study, 8 pediatric patients were treated with 15 $\mu\text{g/kg/day}$ of octreotide administered as an injection 3 times daily and exhibited a weight loss of -4.8 ± 1.8 kg over 6 months [28]. A subsequent double-blind study enrolled 20 patients. The 9 patients who were treated with octreotide had an average weight gain of $+1.6 \pm 0.6$ kg (with 1 patient gaining 5.3 kg during the study) and a statistically significant decrease in BMI (i.e., -0.2 ± 0.2 on treatment vs. $+2.2 \pm 0.5$ on placebo) due to the continued linear growth. Additionally, all subjects treated with octreotide developed diarrhea and abdominal discomfort; 44% developed gallbladder sludge or true cholelithiasis on ultrasound, requiring adjunct therapy with ursodiol. Two patients developed an impaired glucose tolerance, and 1 patient developed type 2 diabetes during the open-label extension [28]. Other isolated case reports have demonstrated a slower weight gain but no significant weight loss on therapy [31]. A

multicenter trial in pediatric patients (age 6–18 years) coordinated by Novartis Pharmaceuticals in 2004 failed to elicit change in BMI; the study was terminated (ClinicalTrials.gov identifier: NCT00076362). In addition, the significant side effects have rendered octreotide a difficult medication for long-term adherence.

Diazoxide and Metformin

Considering that isolated therapy targeting β -cells was ineffective, dual therapy with diazoxide and metformin was proposed to lower insulin secretion but mitigate the risk for hyperglycemia [32]. Diazoxide binds to the KATP channel of the β -cell and decreases insulin secretion. Metformin is a unique oral agent that improves insulin sensitivity and decreases hepatic gluconeogenesis. The combination therapy was studied in nine pediatric patients with HO following CP therapy. The synergy of enhanced insulin action and lower insulin levels resulted in a decreased weight gain of $+1.2 \pm 5.9$ kg compared to $+9.5 \pm 2.7$ kg in the 6 months prior to therapy. Of the 7 patients who completed the study, the 2 with the highest pretreatment insulin levels responded with the most robust weight loss [32]. The study was limited by its small size and notable adverse events, with 1 patient withdrawing due to development of peripheral edema and another due to emesis and elevated liver enzymes.

Metformin and Fenofibrate

Combination therapy with metformin and fenofibrate was studied in 22 children following CP therapy [33]. Fenofibrate is a peroxisome proliferator-activated receptor- α (PPAR α) agonist; this is expressed throughout the body and has been implicated in improved insulin sensitivity [34] as well as decreased triglycerides. The patients did not have significant improvement in weight or BMI and instead had an increase in BMI during the 6-month study; however, they did have improved lipid profiles and insulin resistance.

Surgical Approaches

Vagotomy

Truncal vagotomy has been used in patients with essential obesity to limit insulin secretion due to vagal stimulation. As reported in a 1983 case report, this surgical approach to address the hyperinsulinism associated with HO was used in a 19-year-old woman and resulted in an 11-kg weight loss over 2 years. The patient had improved satiety and insulin sensitivity; weight was not regained [35].

Gastric Bypass

Bariatric surgery is designed to restrict the food intake via a decrease in gastric volume as well as to create some malabsorption through Roux-en-Y anastomosis. The first HO patient treated with Roux-en-Y also had truncal vagotomy. That patient is reported as maintaining a BMI of 50 2.5 years after his surgery (the BMI was 25 at diagnosis and peaked at 63 prior to surgery) [31]. A meta-analysis of 21 CP survivors (8 of whom were adolescents) with HO who underwent gastric bypass showed varying degrees of weight loss and a lowest postsurgery BMI of 34 [36]. The Roux-en-Y procedure was found to be superior to gastric banding or sleeve gastrectomy. It is important to note that the meta-analysis followed patients only up to 1 year from surgery and relied on communication with the surgical teams, leading to reporting bias. The study authors reported encouraging 1- and 2-year data in adolescents using Roux-en-Y; however, there are still some treatment-resistant patients [31, 37]. Roux-en-Y has been reported to be superior to other bariatric procedures in treating HO as compared to patients with severe obesity. However, the HO patients tended to have lower weight loss overall at 2 years [38]. In addition, due to permanent alteration of the normal physiologic nutrient absorption as well as complications of bariatric surgery, there are ethical concerns regarding offering this procedure in the pediatric population [8].

Targeting Energy Expenditure/Anorectic Drugs

Tri-Iodothyronine Monotherapy

Tri-iodothyronine (T3) increases energy expenditure via thyroid hormone-induced thermogenesis. In murine studies, T3 increased brown adipose tissue (BAT) activity through sympathetic neural stimulation of the hypothalamus. In a reported case series, 3 patients (1 adult and 2 children) exhibited weight loss and a reduction of daytime lethargy with T3 supplementation for up to 2 years [39]. Those patients had suprasellar tumors (astrocytoma, optic glioma, and mixed germ cell) but not CP. It is unclear whether they had significant hypothalamic damage. Adults with subclinical hyperthyroidism have a decreased bone mineral density; however, the adult patient was shown to have an improved bone mineral density over the 27 months of therapy. Supplementation of traditional levothyroxine hormone replacement with T3 has not been pursued in the treatment of HO. Subsequent to this publication, van Santen et al. [40] measured the metabolic BAT activity in a patient with HO following CP treated with T3. Perhaps because the hypothalamic pathways were damaged, no changes in energy expenditure or BAT activity were seen, suggesting that this adjunct therapy is not beneficial.

CNS Stimulants

Dexamphetamine. Most commonly used for the treatment of attention deficit disorder, dexamphetamine has also been used to decrease appetite and improve concentration in patients with HO. In a series of 12 patients treated for an average of 13 months, dexamphetamine improved daytime wakefulness and resulted in weight loss or weight stabilization [41]. Similarly, dextroamphetamine resulted in weight stabilization in 5 patients treated for 24 months [42].

Sibutramine. Sibutramine, a serotonin and noradrenaline reuptake inhibitor, is also known to decrease appetite and prevent a decrease in energy expenditure after weight loss [43, 44]. Sibutramine induced weight loss in children with HO but its efficacy was reduced compared to non-HO [45]. Further studies are unlikely as sibutramine was withdrawn from the USA and other major markets in 2010 due to concerns regarding an increased cardiovascular risk [46].

Caffeine and Ephedrine. A hallmark of HO is reduction of the sympathetic nervous system tone. Medications that increase energy expenditure could be effective in reducing weight gain in HO. A combination of caffeine and ephedrine was used in 3 patients with a mean weight loss of 13.9% [47]. This drug combination is known to induce weight loss; ephedrine increases energy expenditure and reduces appetite by stimulating β -adrenergic receptors and caffeine potentiates the effects by blocking the inhibitory effects of adenosine [48–50]. A main concern of stimulant medications is tachyphylaxis, but these 3 patients were able to maintain the weight loss for several years.

GLP1RA

Many antiobesity drugs require intact hypothalamic signaling pathways for appetite inhibition, and, for such medications, weight reductions in obese children suffering from CP were poor compared to uncomplicated obesity [45]. Importantly, the satiating effect of gut peptides, such as cholecystokinin and glucagon-like peptide-1 (GLP-1), is titrated to the overall state of energy balance through hypothalamic actions of circulating leptin and insulin [51]. As HO subjects have intact hindbrain weight homeostatic structures [52], their high circulating leptin [53, 54] can bind to hindbrain receptors, theoretically leading to an amplification of GLP-1 effects on energy intake and homeostasis.

HO subjects might experience an increased sensitivity to GLP-1 receptor analog (GLP1RA) treatment. A novel HO rat model that recapitulates the most common clinical and biochemical HO features was developed [55, 56].

The HO rats were treated with GLP1RA. Interestingly, a stronger reduction in food intake was found in rats who received exendin-4 compared to those who received saline injections in both lesioned rats and controls (difference between saline- and exendin-4-injected rats: lesion -20.8% , $p = 0.001$, control -13.6% , when adjusted for the effect of saline injection) [57], supporting this theory.

Studies looking at GLP1RA administration have shown varying degrees of success. In a small adult study, 9 patients with HO following tumors had a sustained weight loss (-13.1 ± 5.2 kg over 6–51 months) when treated with GLP1RA [58]. It is important to note that 8 of the patients in that study had developed type 2 diabetes. In a separate adult study, 8 adult patients with HO, but not diabetes, were treated with twice-daily exenatide for a year and 6 of the 8 patients were found to be losing weight but there was no significant weight loss overall (-1.4 ± 4.3 kg) [59].

Methionine Aminopeptidase Inhibitor

Methionine aminopeptidase 2 inhibitors were initially developed as antiangiogenesis tumor therapy. The medication was subsequently found to cause weight loss with increased adiponectin and decreased leptin, leading to decreased lipogenesis, increased fat oxidation, and increased lipolysis. The mechanisms behind this are unclear but they are proposed to be due to changes in extracellular signal-regulated kinase hypophosphorylation. A study looking at 14 adult patients with HO, treated for 8 weeks (the first 4 weeks were placebo controlled) showed an average decrease in body weight of 3.2 kg in the first 4 weeks and 6.2 kg at 8 weeks [60]. Additionally, patients were found to have significantly decreased leptin levels after 4 weeks of therapy. Unfortunately, although the weight loss was consistent, and seen in all of the patients treated, the development of this medication was stopped due to venous thromboembolic events seen in other clinical studies with the methionine aminopeptidase 2 inhibitor [61].

Oxytocin

Oxytocin is a neuropeptide synthesized in the hypothalamus. The peptide has been shown to have anorexigenic effects through oxytocin receptors in the brain and vagal afferents in the nucleus solitarius (hindbrain), as well as some peripheral effects on brown fat oxidation. Sustained oxytocin administration has been shown to induce weight loss through a reduced food intake, increased energy expenditure, and lipolysis [62]. A single dose of intranasal oxytocin has been shown to improve insulin sensitivity. A recent case report showed sustained weight loss with combination therapy using intranasal oxytocin and naltrexone [63].

Current Research and Future Directions

HO following tumor invasion of the hypothalamus is one of the most refractory forms of childhood obesity and leads to an increased risk for metabolic syndrome and cardiovascular disease [64]. It is not sufficient to replace the deficient pituitary and further downstream hormones as, even with proper hormonal replacement, damage to the mediobasal hypothalamus disrupts the integration of peripheral hormonal signals and central neuropeptides, ultimately resulting in inappropriate food intake and weight gain. Therefore, new interventions targeting the hypothalamic signaling pathways balancing anorexigenic and orexigenic neuropeptides are necessary for HO management in order to achieve sustained weight loss. In addition, the development of drugs that can safely increase and normalize energy expenditure are warranted as well, i.e., increasing BAT growth and stimulation. Research in this area is urgently needed to find a therapy, potentially combining multiple treatment strategies across a variety of disciplines in order to combat this treatment-resistant form of severe obesity. In order to address the heterogeneity of different pathophysiological problems leading to HO in patients with CP or other suprasellar tumors, Iersel proposed an individualized treatment algorithm addressing 6 domains, i.e., hyperphagia, decreased energy expenditure, hyperinsulinemia, hypopituitarism, sleep disturbances, and psychosocial disorders. In order to treat HO, an individualized plan of combined interventions of increased physical activity guided by an exercise physiologist, and lifestyle and dietary changes, in addition to specific pharmacological interventions, may be necessary and it may even include bariatric surgery for some patients [65].

A search of ClinicalTrials.gov points to 3 studies on HO currently recruiting. There are no current studies listed for bariatric surgery in HO. An ongoing crossover pilot study led by Dr. Shana McCormack [66] is investigating intranasal oxytocin for therapy in children with HO following suprasellar tumors (ClinicalTrials.gov identifier: NCT02849743). Considering that oxytocin has effects outside of the hypothalamus, there is potential for a therapeutic benefit in the HO population. This study, with a target enrollment of 30 patients, will examine changes in weight after 8 weeks of intranasal oxytocin versus placebo.

There are currently 2 studies using GLP1RA therapy. As with the oxytocin study, these efforts are directed at bypassing the damaged pathways and using pharmacologic doses of GLP1RA to target hindbrain receptors. A multicenter, randomized clinical trial is underway to assess the efficacy

and safety of weekly exenatide in patients aged 10–25 years with HO (ClinicalTrials.gov identifier: NCT0266444). An additional multicenter study is underway in France (ClinicalTrials.gov identifier: NCT02860923) using twice daily exenatide in patients with HO aged 17–75 years.

Conclusions

The hypothalamus plays a fundamental role in translating multiple afferent signals into autonomic efferent signals for energy balance. This results in alterations in gene expression of key neuropeptides involved in the regulation of energy storage and expenditure. Children who suffer from HO have sustained damage to the afferent signaling of hormones and the autonomous nervous system. They no longer have the necessary nuclei to coordinate and regulate secretion and signal transduction of key peptides that act in concert to modulate energy homeostasis, such as NPY, α -melanocyte-stimulating hormone, oxytocin, melatonin, 5HT, dopamine, leptin, GLP-1, PYY, ghrelin, and insulin. There are new and promising approaches, such as oxytocin treatment or utilization of intact hindbrain signaling with GLP1RA therapy, but results from randomized clinical trials are pending. There is a need for more research in bypassing/circumventing this central damage to create new afferent signaling pathways and integration of the ubiquitous signals. Perhaps it is also the case that a single therapy will be insufficient to replace the various and yet nonredundant hypothalamic mechanisms of disturbed energy homeostasis and that a more prudent direction would be to examine the effectiveness of combinations of agents and/or surgical therapies.

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The authors have no ethical conflicts to disclose.

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Drs. Abuzzahab, Roth, and Shoemaker collaboratively drafted, reviewed, and revised this paper. All of the authors approved the final version of this paper as submitted and agree to be accountable for all aspects of this work.

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