2 Central Control of Energy Metabolism and Hypothalamic Obesity

Belma Haliloglu and Abdullah Bereket

Hypothalamic Regulation of Energy Storage and Expenditure

The hypothalamus is the primary center controlling energy intake, expenditure, and storage. The mission of energy balance is executed via afferent and efferent signals. Afferent signals received from peripheral tissues including white adipose, pancreas, liver, and the gastrointestinal tract are processed and interpreted in the hypothalamus. Signals originating in the hypothalamus are delivered to organs and tissues via efferent signals. Earlier studies identified the ventromedial hypothalamus (VMH) and the lateral hypothalamic area (LHA) as the satiety and feeding centers of the brain, respectively. However, recent investigations have increased our understanding of hypothalamic structure and function and now identify major areas for energy regulation in the paraventricular nuclei (PVN) and arcuate nucleus (ARC) as well as VMH and LHA (Fig. 2.1) [1, 2].

B. Haliloglu, MD
Department of Pediatrics/Pediatric Endocrinology, Yeditepe University, Içerenköy, Yeditepe Unv. Hst., 34752 Ataşehir, Istanbul, Turkey

A. Bereket, MD (✉)
Department of Pediatrics/Pediatric Endocrinology, Marmara University, Fevzi Çakmak Mahallesi, Mimar Sinan Caddesi
No. 41, Ustakaynarca-Pendik, Istanbul, Turkey
e-mail: abdullahbereket@gmail.com

The ARC consists of two groups of neurons: the orexigenic neurons that secrete agouti-related protein (AgRP) and neuropeptide Y (NPY) and the anorexigenic neurons that secrete proopiomelanocortin (POMC) and cocaine-amphetamine-related transcript (CART). AgRP/NPY and POMC/CART neurons function as sensors of peripheral tissues, responding to nutrient, neuronal, and hormonal signals including glucose, amino acids, short-chain fatty acids, adipocytokines (such as leptin), ghrelin, insulin, and the gastrointestinal hormones [3, 4].

POMC is cleaved by prohormone convertases (PC1/PC3, PC2) and processed via tissue-specific posttranslational modification. In the hypothalamus, POMC cleavage generates a variety of peptides including ACTH, melanocyte-stimulating hormone (MSH), beta-lipotropin, endorphins, and corticotropin-like intermediate lobe peptide (CLIP) [4]. α-MSH binds as an agonist to melanocortin receptors 3 and 4 (MC3R/MC4R) in PVN neurons and inhibits food intake. Conversely, AgRP promotes food intake by antagonizing MC3R/MC4R signaling and inhibits energy expenditure. NPY also stimulates food intake via binding to Y receptors in the PVN [4, 5].

Peripheral hormones and cytokines, including leptin, ghrelin, insulin, and glucagon-like peptide 1 (GLP-1), play central roles in this system. Ghrelin stimulates appetite and food intake by activating NPY neurons in the ARC and mimics

M.S. Freemark (ed.), *Pediatric Obesity*, Contemporary Endocrinology,
https://doi.org/10.1007/978-3-319-68192-4_2

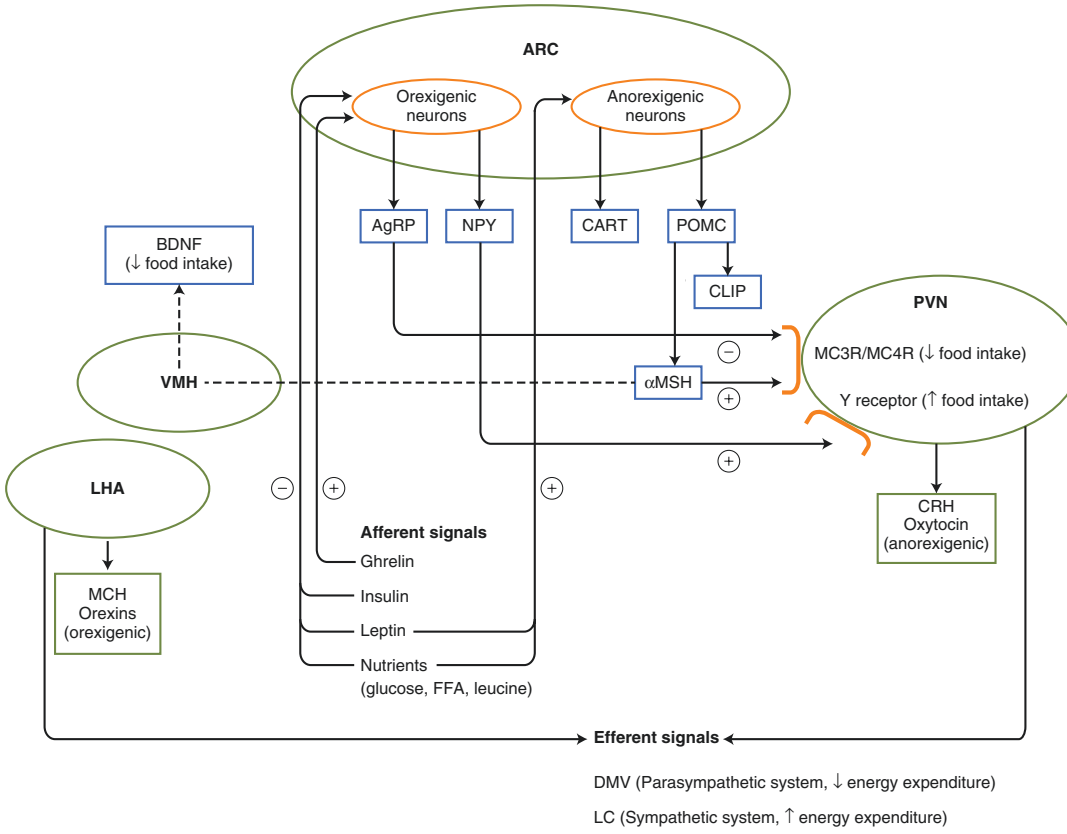

Fig. 2.1 A simplified scheme of regulation of energy homeostasis by the hypothalamus. *ARC* arcuate nucleus, *PVN* paraventricular nucleus, *VMH* ventromedial hypothalamus, *LHA* lateral hypothalamic area, *AgRP* agouti-related peptide, *NPY* neuropeptide *Y*, *CART* cocaine-amphetamine-related transcript, *POMC* proopiomelanocortin, *CLIP* corticotropin-like intermediate lobe peptide, *α-MSH* alpha-melanocyte-stimulating hormone, *BDNF* brain-derived neurotrophic factor, *MCH* melanin-concentrating hormone, *CRH* corticotropin-releasing hormone, *DMV* dorsal motor nucleus of the vagus, *LC* locus coeruleus

the effect of NPY in the PVN [5]. In contrast, insulin (administered centrally) and leptin suppress the expression of AgRP and NPY [6]. At the same time, leptin stimulates the expression of POMC and CART and thereby limits the drive to feed [2].

Although insulin and leptin receptors are localized in a variety of brain areas, the ARC is adapted for sensing of additional hormone and nutrient signals by virtue of its having a relatively permeable blood-brain barrier [6]. The ARC responds to glucose, oleic acid, leucine, and GLP-1, which is derived from proglucagon in the L cells of the ileum and colon. GLP-1 reduces food intake through both peripheral (vagal) and central mechanisms (see also Chap. 3 on GI Hormones and the Control of Food Intake and Energy Metabolism). In addition to mediating the anorexic effect of GLP-1, the ARC GLP-1 receptor also binds oxyntomodulin (OXM), another anorexigenic peptide derived from proglucagon. Peptide YY (PYY, peptide tyrosine-tyrosine), which is also released from intestinal L cells, decreases food intake through its interaction with NPY receptors in the ARC [6].

While the ARC is the key area for the regulation of energy homeostasis, the VMH, PVN, and LHA have important functions as well. The VMH contains neurons sensitive to glucose and other feeding-related stimuli. The VMH also responds to melanocortins, which reduce

food intake in part through induction of brain-derived neurotrophic factor (BDNF) [1, 2]. Intracerebroventricular injection of BDNF inhibits feeding and reduces mesenteric fat mass in Goto-Kakizaki rats [7]. The PVN has an anorexigenic action that is effected via secretion of CRH and oxytocin and expresses both MC3R/MC4R and Y receptors [2]. Conversely, the LHA has an orexigenic effect and secretes anabolic peptides such as melanin-concentrating hormone and orexins [3, 8]. Orexins are induced by fasting and promote arousal, feeding behavior, brown adipogenesis, lipogenesis, emotional memory, and autonomic nervous system activity [9].

The activity of the autonomic nervous system is integrated with hypothalamic signaling to modulate energy balance. The PVN and LHA send impulses to the dorsal motor nucleus of the vagus (DMV) and the locus coeruleus (LC) for control of the parasympathetic (PNS) and sympathetic nervous systems (SNS), respectively. While anorexigenic signals activate the SNS via the LC and increase energy expenditure, orexigenic signals send projections to the DMV and promote energy deposition [10]. Gastrointestinal satiety hormones (including cholecystokinin, GLP-1, and PYY) that are secreted in response to dietary lipid or protein can activate receptors on local sensory nerves in the duodenum and signal to the hypothalamus via the vagus nerve [6] (see Chap. 3).

Genetic defects in the peptides, enzymes, or receptors in these pathways, or damage to their neural circuits, can lead to hypothalamic obesity (HyOb, Table 2.1) (see a more detailed discussion in Chap. 8 on Monogenic Obesity and Chap. 9 on Syndromic Obesity).

Pathophysiologic and Metabolic Features of Hypothalamic Obesity

Biochemical features of HyOb include hyperleptinemia, hyperinsulinemia, sympathetic nervous system (SNS) dysregulation, enhanced white adipose 11β-hydroxysteroid dehydrogenase-1 (11β-HSD1) activity, and impaired melatonin signaling.

Table 2.1 Etiology of hypothalamic obesity

Structural causes	Functional causes
— *Brain tumors*	— *Genetic causes*
Craniopharyngioma	Leptin (LEP)
Glioma	Leptin receptor (LEPR)
Germinoma	MC4R
Ependymoma	POMC
Meningioma	CART
Hamartoma	Prohormone convertase-1
Pinealoma	TrkB, NTRK2
Endothelioma	BDNF
Colloid cysts	SIM-1
Pituitary macroadenoma	SH2B1
Leukemia	KSR2
Langerhans cell histiocytosis	TUB
Teratoma	
Metastasis	
	— *Syndromes*
— *Inflammatory*	Prader-Willi syndrome
Sarcoidosis	Bardet-Biedl syndrome
Tuberculosis	ROHHAD
Arachnoiditis	
Encephalitis	— *Psychotropic drugs*
Histiocytosis X	(Antidepressants, mood stabilizers, antipsychotics)
— *Neurosurgery*	
— *Cranial radiotherapy*	

Hyperleptinemia

Leptin levels rise in "exogenous" obesity in proportion to white adipose tissue mass. In response to progressive weight gain, the transport of leptin into the CSF plateaus, and there is partial inhibition of central leptin signaling; in combination, these blunt the anorectic effect of leptin in severe obesity. Patients with hypothalamic damage or genetic defects in leptin or the leptin receptor have even greater impairment in leptin action; this promotes food-seeking behavior and limits energy expenditure, leading to massive weight gain and fat deposition [3]. Except in patients with leptin gene mutations, the levels of leptin in children with HyOb are higher than in BMI-matched patients with common exogenous obesity [11].

Hyperinsulinemia

The hypothalamus controls pancreatic insulin release via α-MSH activation of the sympathetic system and vagal stimulation [10, 12]. Damage to the hypothalamus is associated with hyperinsulinemia, weight gain, and glucose intolerance [13]. Conversely, insulin acts centrally to suppress food intake and weight gain [10, 14]. The hyperinsulinemia of HyOb results from defects in α-MSH signaling, vagal hyperactivity, and loss of central insulin signaling [10]. Although some studies showed similar fasting insulin levels in HyOb and BMI-matched obese patients [11, 15], the insulin secretory response to glucose is exaggerated in children with HyOb and is generally higher than expected for their BMIs (Table 2.2) [11, 13].

Hyperinsulinemia promotes lipogenesis and inhibits lipolysis and may thereby induce, or exacerbate, weight gain in children with HyOb. It has been proposed that hyperinsulinemia (and weight gain) may maintain linear growth in GH-deficient children following hypothalamic surgery, the so-called growth without growth hormone [16].

Dysregulation of Autonomic Nervous System Activity

Experimental and clinical studies establish strong and reciprocal links between autonomic nervous system activity and HyOb. Lesions of the VMH and LHA in experimental animals cause HyOb via increased parasympathetic tone, decreased sympathetic activity, reduced thermogenesis, and decreased mobilization of fatty acids [12]. Likewise, post-op craniopharyngioma patients with obesity had lower urinary catecholamine metabolites (homovanillic acid, HVA, and vanillylmandelic acid, VMA), lower morning heart rates, and lower activity scores; those with highest BMI had the lowest urinary HVA and VMA [17]. ARC neurons expressing CART likely play a role in regulation of autonomic activity: central

Table 2.2 Metabolic features of hypothalamic obese (HyOb), hypothalamic nonobese (HyNOb), and simple obese (Ob) children

	HyOb	HyNOb	Ob	*p*
n	23	16	22	
Gender (M/F)	11/12	5/11	10/12	NS
Age (years)	10.3 (8–14.6)	11.4 (8.9–14.1)	10.8 (8.9–12.8)	NS
BMI-SDS	2.0 (1.5–2.1)	0.18 (−0.5–0.56)	2.1 (1.8–2.3)	<0.001 (HyNOb vs. HyOb, Ob)
Leptin (ng/mL)	89.2 (40.7–143.6)	25.3 (13.3–53.3)	66 (48–90)	<0.05 (HyNOb vs. HyOb, Ob)
Leptin/BMI	4.0 (1.6–5.2)	1.5 (0.8–3.1)	2.5 (1.8–3.5)	<0.05 (HyOb vs. HyNOb, Ob)
sOb-R (ng/mL)	46.3 (36.1–53.5)	44 (36.9–59.8)	40.3 (34.1–51.8)	NS
Leptin/sOb-R (FLI)	2.0 (0.8–3.5)	0.6 (0.3–1.2)	1.5 (1–2.3)	<0.05 (HyNOb vs. HyOb, Ob)
Resistin (ng/mL)	2.6 (1.9–3.1)	2.8 (1.7–3.4)	3.0 (2.2–3.5)	NS
Fasting glucose (mmol/L)	4.3 (3.7–4.6)	4.4 (4–4.9)	5 (4.7–5.3)	<0.05 (Ob vs. HyOb, HyNOb)
120 min glucose in OGTT (mmol/L)	6.1 (5.1–6.5)	5.8 (4.8–6.1)	6.0 (5.6–6.9)	NS
Fasting insulin (mU/L)	16 (9–23)	10 (6.6–16)	28 (19–39)	<0.05 (Ob vs. HyOb, HyNOb)
120 min insulin in OGTT (mU/L)	58.5 (42–70)	33 (12–49.5)	78 (51–92)	<0.05 (Ob vs. HyNOb)
% change of insulin during OGTT	259 (162–411.5)	152 (50–327.5)	161 (79.5–221.5)	<0.05 (Ob vs. HyOb)
HOMA-IR	2.8 (2–4.3)	1.8 (1.2–3)	6.5 (3.9–8.5)	<0.05 (Ob vs. HyOb, HyNOb)

sOb-R (soluble leptin receptor) and FLI (free leptin index)

Used with permission of Springer Science from Guran T, Turan S, Bereket A et al. The role of leptin, soluble leptin receptor, resistin, and insulin secretory dynamics in the pathogenesis of hypothalamic obesity in children. Eur J Pediatr 2009; 168: 1043–1048

administration of CART increases uncoupling protein levels and thermogenesis in brown adipose tissue via the sympathetic nervous system (SNS) [18].

Melatonin Dysregulation

Through release of norepinephrine, the SNS controls the release of melatonin from the pineal gland. In one study HyOb patients had lower morning and nighttime salivary melatonin levels, which were related inversely to BMI [19]. In animal studies, melatonin administration has been shown to decrease adiposity, leptin levels, and body weight and to reduce insulin secretion via pancreatic melatonin receptors (MT1 and MT2) [20, 21]. Spontaneous physical activity and core body temperature are increased and the relative weight of intra-abdominal fat is reduced. Thus decreases in melatonin secretion may contribute to, or exacerbate, the hyperinsulinemia and weight gain of patients with HyOb.

11β-Hydroxysteroid Dehydrogenase-1 (11β-HSD1)

After extensive suprasellar operations for resection of hypothalamic tumors, some patients develop Cushing-like morbid obesity, while they receive replacement doses of glucocorticoids. It was hypothesized that target tissue conversion of inactive 11-ketosteroids to active 11β-OH glucocorticoids might explain the obesity of some patients with hypothalamic lesions. 11β-HSD1 catalyzes the transformation of inactive cortisone to active cortisol in white adipose tissue, liver, and skeletal muscle. Overexpression of 11β-HSD1 in white adipose tissue is accompanied by abdominal adiposity and features of the metabolic syndrome. Tiosano and colleagues studied ten patients with hypothalamic obesity and secondary adrenal insufficiency and six control Addisonian patients while they were on glucocorticoid replacement therapy. They found increased 24 h urine-free cortisol to cortisone ratio in HyOb patients after a single oral dose of 12 mg/m^2 hydrocortisone acetate, with a positive correlation between urine cortisol/cortisone and the ratio of visceral fat to subcutaneous fat [22]. The authors proposed that a deficiency of hypothalamic messengers after surgical injury enhances glucocorticoid activity in visceral white adipose via upregulation of 11β-HSD1 activity. The exact mechanism by which hypothalamic obesity upregulates visceral 11β-HSD1 activity is not well understood. However, ACTH, CRH, and α2-adrenergic stimulation diminish 11β-HSD1 activity in human adipocyte cultures, whereas β2-adrenergic stimulation and inflammatory cytokines (such as TNFα and IL-1β) upregulate 11β-HSD-1 activity [23].

Etiology of Hypothalamic Obesity

The causes of HyOb may be classified in two broad categories. Damage causing disruption of hypothalamic pathways can be *structural*, as seen in hypothalamic tumors prior to, and more commonly after, neurosurgery, inflammatory disorders, radiotherapy, or trauma. Alternatively, it can represent a *genetic or syndromic disorder* such as rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD) syndrome or the Prader-Willi syndrome (Table 2.1).

Craniopharyngioma (CF)

The most common cause of HyOb is acquired structural hypothalamic damage; among its causes, the best known and most extensively studied is craniopharyngioma. The diagnosis of craniopharyngioma in children is often delayed, so the major manifestations are visual impairment (62–84%) and neuroendocrine deficits (52–87%) [24]. Detailed assessment of the initial MRI can delineate the extent of hypothalamic involvement and predict the likelihood of subsequent HyOb (see below). The prevalence of HyOb has been reported to be as high as 55% after surgical treatment of craniopharyngioma [24, 25]. Suprachiasmatic lesions are associated with even

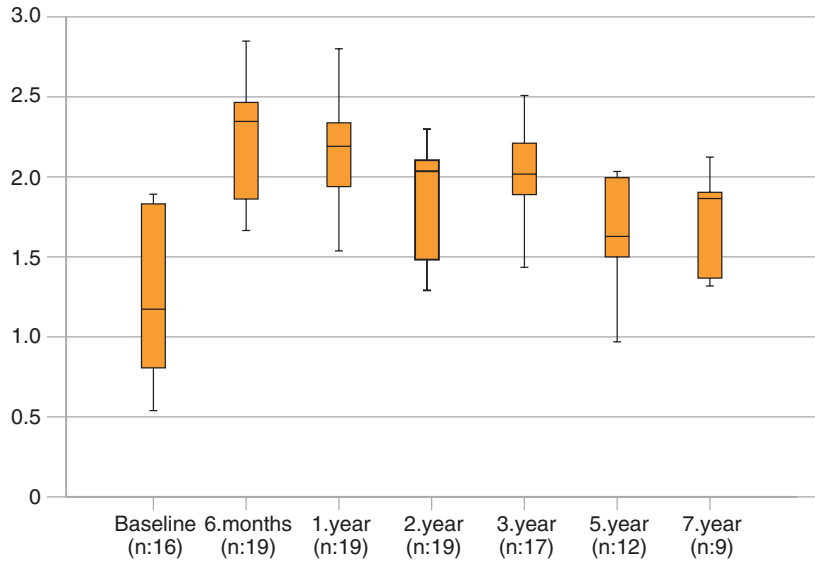

Fig. 2.2 Mean BMI-SDS during 7 years of follow-up in patients with hypothalamic obesity. The boxes represent interquartile range (25–75%) (Used with permission of John Wiley and Sons from Haliloglu B, Atay Z, Guran T, Abali S, Bas S, Turan S, Bereket A. Risk factors for mortality caused by hypothalamic obesity in children with hypothalamic tumours. Pediatric Obesity 2016 11(5):383–8)

higher morbidity rates; surgical removal of tumors beyond the mammillary bodies places the child at very high risk of HyOb [26].

HyOb is associated with rapid weight gain during the first 6 months after surgery; this is commonly followed . by stabilization of weight [25, 27] (Fig. 2.2). Factors predicting the development of HyOb include age <5–6 year at diagnosis, tumor histology (craniopharyngioma, optic glioma), hypothalamic tumor involvement, radiotherapy (>51 Gy), third ventricle hydrocephalus, and the presence of hypothalamic endocrinopathy [25, 27, 28] (Table 2.3). Weight gain often persists or progresses despite hormone replacement therapy.

Table 2.3 Predictive factors for the development of HyOb

Predictive factors for the development of HyOb
— Hypothalamic involvement
— Young age (<5–6 years) at diagnosis
— Histology of tumor
— Radiotherapy (>51 Gy)
— Presence of hypothalamic endocrinopathology
— Hydrocephalus requiring ventriculoperitoneal shunt

Acute Lymphoblastic Leukemia (ALL)

Although obesity is a common complication of childhood ALL, with a prevalence ranging from 9 to 48%, HyOb is not common [29]. Factors contributing to obesity in ALL include sedentary behavior, radiotherapy-induced hypothalamic damage, chemotherapy, growth hormone deficiency, and corticosteroid therapy [14, 29]. Cranial irradiation and intrathecal chemotherapy can cause hypothalamic damage, leading to hormonal deficiencies and hypothalamic dysregulation of food intake. Increases in fat deposition usually emerge during the first year of therapy and often persist during subsequent years. Female gender and ≥20 Gy cranial radiation therapy seem to be risk factors for BMI ≥ 30 in several studies [29].

Monogenic and Syndromic Forms of HyOb

A variety of mutations in genes controlling appetite, energy expenditure, and weight gain can cause early-onset obesity in children. *These are described in detail in Chap. 8 on Monogenic Obesity by David Meyre and Marie Pigeyre*. Likewise, a number of genetic syndromes associated with hypothalamic dysfunction cause early- or late-onset childhood obesity; these are discussed in Chap. 9 on Syndromic Obesity by Krystal Irizarry and Andrea Haqq. In Table 2.4

Table 2.4 Genetic causes of HyOb and clinical features

Gene	Function	Phenotype
LEP[a]	Anorexigenic effect	Severe obesity, hyperphagia, hypogonadism, normal height until puberty but short stature after puberty
LEPR[b]	Leptin signaling	Severe obesity, hyperphagia, hypogonadism hypothyroidism, growth retardation (low IGF1, IGFBP3)
MC4R[c]	α-MSH signaling	Severe obesity, increased linear growth, hyperphagia, severe hyperinsulinemia
POMC[d]	Precursor of α-MSH	Early-onset obesity, red hair, central adrenal insufficiency
CART[e]	Anorexigenic effect	Childhood and adult obesity in heterozygotes
PCSK1[f]	Cleaving of POMC to α-MSH	Obesity, central adrenal insufficiency, hypogonadism, impaired glucose tolerance, postprandial hypoglycemia, severe malabsorptive neonatal diarrhea
TrkB and NTRK2[g]	TrkB is the receptor for BDNF, NTRK2 codes a subunit for TrkB	Obesity, hypotonia, developmental delay, impaired short-term memory and decreased nociception
BDNF[h]	Regulation of MC4R signaling	Haploinsufficiency of BDNF detected in WAGRO syndrome
SIM-1[i]	Formation of PVN	Obesity, hyperphagia, developmental delay
SH2B1[j]	Modulation of tyrosine kinases or JAK-associated cytokine receptors	Early-onset obesity, hyperphagia, disproportionate insulin resistance, reduced final height, behavioral abnormalities
KSR2[k]	Intracellular protein involved in multiple signaling pathways	Hyperphagia, obesity, low heart rate, reduced basal metabolic rate, severe insulin resistance
TUB[l]	Control in insulin and leptin signaling and action in vivo hypothalamic nuclei	Obesity, retinal dystrophy
ch15q11–13 (PWS)[m]	Lack of paternally imprinted genes on ch15q11–13	Hyperphagia, severe obesity, short stature, hypogonadism hypotonia, hyperghrelinemia
Several genes[n] (BBS)[o]	Cilia function, intracellular protein trafficking, hypothalamic leptin receptor signaling	Obesity, retinitis pigmentosa, polydactyly, hypogonadism
Unknown (ROHHAD)[p]		Rapid-onset obesity, hypothalamic dysfunction, hypoventilation, autonomic dysfunction, and neural tumor

[a]Doche ME, Bochukova EG, Su HW, Pearce LR, Keogh JM, Henning E, et al. Human SH2B1 mutations are associated with maladaptive behaviors and obesity. J Clin Invest. 2012; 122(11): 4732–6

[b]Pearce LR, Atanassova N, Banton MC, Bottomley B, van der Klaauw AA, Revelli JP, et al. KSR2 mutations are associated with obesity, insulin resistance, and impaired cellular fuel oxidation. Cell. 2013; 155(3): 765–77

[c]Borman AD, Pearce LR, Mackay DS, Nagel-Wolfrum K, Davidson AE, Henderson R, et al. A homozygous mutation in the TUB gene associated with retinal dystrophy and obesity. Hum Mutat. 2014; 35(2): 289–93

[d]Goldstone AP, Holland AJ, Hauffa BP, Hokken-Koelega AC, Tauber M. Recommendations for the diagnosis and management of Prader-Willi syndrome. J Clin Endocrinol Metab 2008; 93: 4183–4197

[e]Seo S, Guo DF, Bugge K, Morgan DA, Rahmouni K, Sheffield VC. Requirement of Bardet-Biedl syndrome proteins for leptin receptor signaling. Hum Mol Genet 2009; 18: 1323–1331

[f]Patwari PP, Wolfe LF. Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation: review and update. Curr Opin Pediatr 2014; 26(3): 487–92

[g]Farooqi IS. Monogenic human obesity. Front Horm Res 2008; 36: 1–11

[h]Manzardo AM, Johnson L, Miller JL, Driscoll DJ, Butler MG. Higher plasma orexin A levels in children with Prader-Willi syndrome compared with healthy unrelated sibling controls. Am J Med Genet A. 2016 Aug;170(7):2097–102

[i]Goldstone AP, Patterson M, Kalingag N et al. Fasting and post-prandial hyperghrelinemia in Prader-Willi syndrome is partially explained by hypoinsulinemia, and is not due to peptide YY 3–36 deficiency or seen in hypothalamic obesity due to craniopharyngioma. J Clin Endocrinol Metab 2005; 90: 2681–2690

[j]Dhondt K, Verloo P, Verhelst H, Van Coster R, Overeem S. Hypocretin-1 deficiency in a girl with ROHHAD syndrome. Pediatrics. 2013; 132(2): e788–92

[k]Jacobson LA, Rane S, McReynolds LJ, Steppan DA, Chen AR, Paz-Priel I. Improved Behavior and Neuropsychological Function in Children With ROHHAD After High-Dose Cyclophosphamide. Pediatrics. 2016 Jul;138(1)

[l]Roth CL, Eslamy H, Werny D, Elfers C, Shaffer ML, Pihoker C, Ojemann J, Dobyns WB. Semiquantitative analysis of hypothalamic damage on MRI predicts risk for hypothalamic obesity. Obesity (Silver Spring). 2015 Jun;23(5):1226–33

Table 2.4 (continued)

[m]Geffner M, Lundberg M, Koltowska-Häggström M, Abs R, Verhelst J, Erfurth EM et al. Changes in height, weight, and body mass index in children with craniopharyngioma after three years of growth hormone therapy: analysis of KIGS (Pfizer International Growth Database). J Clin Endocrinol Metab 2004 Nov; 89(10): 5435–5440

[n]At least 20 BBS genes have been defined and all acts in primary cilia functioning

[o]Srinivasan S, Ogle GD, Garnett SP, Briody JN, Lee JW, Cowell CT. Features of the metabolic syndrome after childhood craniopharyngioma. J Clin Endocrinol Metab 2004; 89: 81–86

[p]Müller HL, Handwerker G, Gebhardt U, et al. Melatonin treatment in obese patients with childhood craniopharyngioma and increased daytime sleepiness. Cancer Causes Control 2006; 17: 583–589

we provide a list of genetic and syndromic causes of obesity associated with hypothalamic dysfunction.

Clinical Features

Accelerated weight gain and severe obesity are the most striking features of HyOb; they are caused by hyperphagia, reduced basal metabolic rate (BMR), and decreased physical activity. The accumulation of fat is usually very rapid; following surgery for craniopharyngioma, there is often a dramatic and progressive increment in BMI during the first 6 months. This is typically followed by a stabilization period with no reduction in BMI [25, 27].

Children with craniopharyngioma have greater risks for metabolic syndrome due to increased abdominal adiposity, higher fasting triglycerides, and lower HDL compared with healthy age-, sex-, BMI-, and pubertal stage-matched controls [30]. Nonalcoholic fatty liver disease (NAFLD) develops in about 50% of patients; the use of stimulants (such as modafinil) for treatment of daytime sleepiness may exacerbate hepatic dysfunction [31].

Interestingly, HyOb may exist in the absence of hyperphagia. Studies comparing children with craniopharyngioma and BMI-matched controls found no differences in eating behavior or the frequency of eating disorders [26]. It should be noted, however, that these studies were conducted months or years after surgical treatment. It is possible that initial weight gain is driven by hyperphagia resulting from hypothalamic damage and high-dose glucocorticoid therapy. Subsequently, obesity may be maintained by a reduction in energy expenditure (BMR and physical activity).

Indeed, physical activity is reduced to a far greater degree in hypothalamic obese patients than in simple obese patients and age-matched controls [3, 24]. It is exacerbated by concomitant visual or neurological problems, increased daytime sleepiness, and disturbances of circadian rhythms. The hypothalamic disturbance in sleep regulation results in low nocturnal and early morning melatonin levels. Based on this information, melatonin administration in children with craniopharyngioma has been suggested to improve physical activity and daytime sleepiness [32]. However, long-term studies are needed to evaluate the effect of the hormone in controlling BMI.

Patients with hypothalamic obesity often have sleep-disordered breathing (SDB), which may be associated with decreased melatonin production, disruption of circadian rhythms, and endocrine dysfunction [19] (see Chap. 28 on Sleep-Disordered Breathing and Sleep Duration in Child Obesity by Drs. Van Eyck and Verhulst). In one study 46% of children with central nervous system neoplasms involving the hypothalamus or thalamus had SDB [33]. Excessive daytime sleepiness and SDB are also common in Prader-Willi syndrome. Thus, routine polysomnography should be considered in children with hypothalamic obesity. Central stimulating agents (dextroamphetamine, methylphenidate) could be beneficial in these patients [34].

Risk Factors and Prevention for HyOb in Craniopharyngioma

As the currently available options are not very successful in treatment of HyOb, determination of risk factors and prevention of obesity are of prime importance. The first 6 postoperative months are crucial for preventing HyOb in

patients undergoing brain tumor surgery (Fig. 2.2). Factors predicting the development of HyOb in children with brain tumors are listed in Table 2.3. Hypothalamic involvement and hence, disturbance in energy balance contribute to the development of severe obesity and might explain why 12–19% of patients with craniopharyngioma develop obesity even before diagnosis. MRI findings at diagnosis can also provide postoperative risk assessment: patients who develop HyOb frequently have lesions involving the third ventricular floor, mammillary bodies, and anterior, medial, and most importantly posterior hypothalamus (Fig. 2.3a–d) [35] The development of

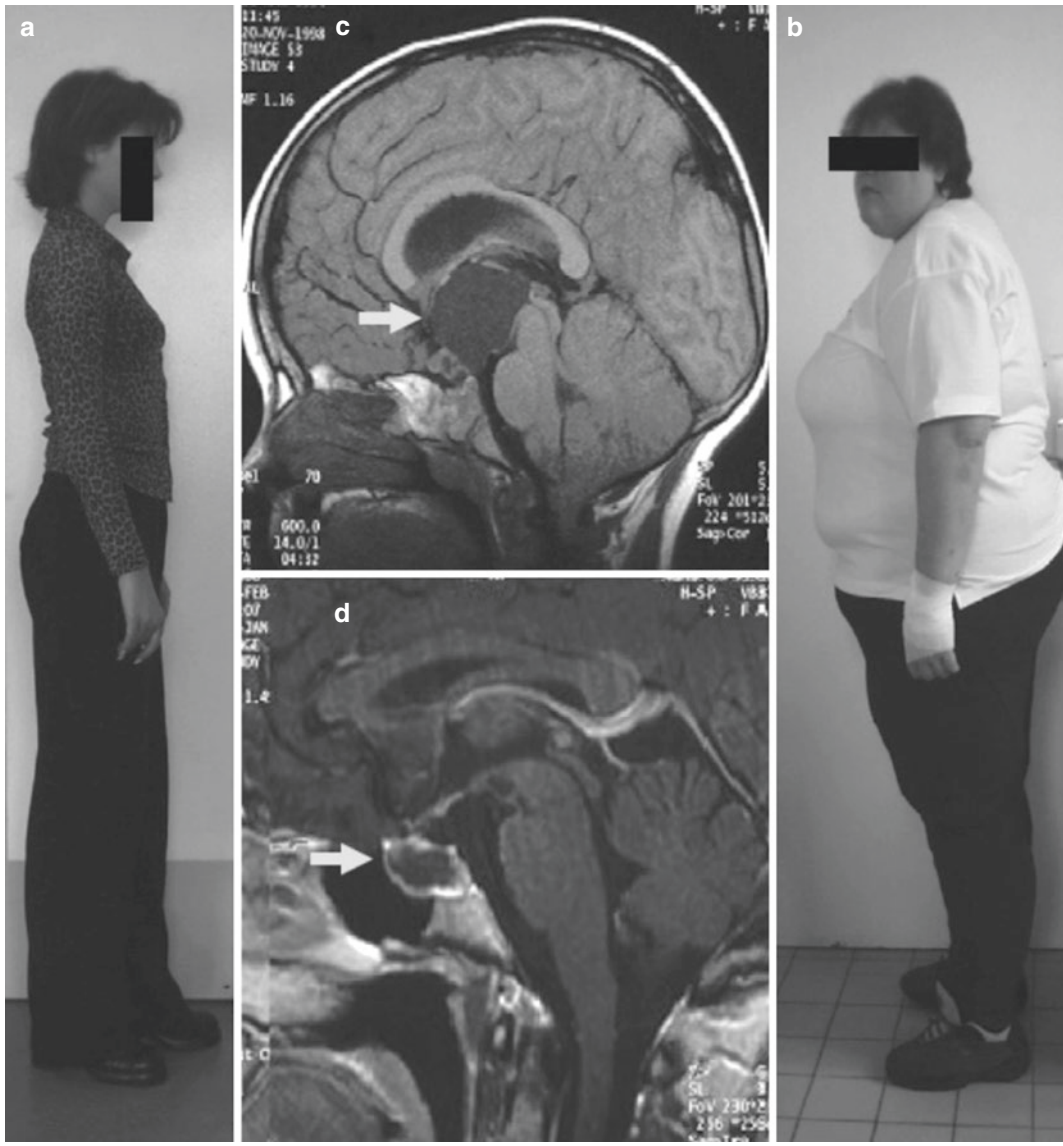

Fig. 2.3 (**a**–**d**) Development of obesity and localization of craniopharyngioma. Postoperatively, both patients had panhypopituitarism. The patient seen in (**a**) had a small tumor revealed by magnetic resonance imaging (MRI) (**d**), which was removed transsphenoidally. Postoperatively, the patient continued to have normal eating behavior, and her weight developed normally (body mass index [BMI]: +1.0 standard deviation [SD]). The patient whose preoperative MRI (**b**) showed a large tumor extending to the suprasellar region and infiltrating the hypothalamus went on to develop an eating disorder and, consequently, obesity (BMI, +14.0 SD) (**c**) (Used with permission of Springer Science from Müller HL et al. Kraniopharyngeom im Kindes- und Jugendalter. Monatsschr Kinderheilkd 2003; 151: 1056–1063)

Table 2.5 Fasting insulin, fasting glucose, resistin, and leptin levels in relation to hypothalamic involvement in HyOb and HyNOb patients

	HyOb			HyNOb		
	With hypothalamic involvement ($n = 17$)	Without hypothalamic involvement ($n = 6$)	p	With hypothalamic involvement ($n = 4$)	Without hypothalamic involvement ($n = 12$)	p
Fasting insulin (mU/L)	16.7 (9.1–24)	13.8 (9.6–16)	0.34	15.1 (10.3–20.2)	9.3 (6.1–13)	0.21
Fasting glucose (mmol/L)	4.3 (3.7–4.4)	4.3 (4–4.7)	0.98	4.4 (4.1–5.3)	4.3 (4–4.7)	0.30
Resistin (ng/mL)	2.8 (2.2–3.1)	1.9 (1.6–2.9)	0.21	2.2 (1.7–2.7)	3 (1.7–3.8)	0.24
Leptin (ng/mL)	119 (73–155)	35.2 (23–67)	0.02	75.7 (25.5–91.6)	17.7 (13–43.5)	0.01

Used with permission of Springer Science from Guran T, Turan S, Bereket A et al. The role of leptin, soluble leptin receptor, resistin, and insulin secretory dynamics in the pathogenesis of hypothalamic obesity in children. Eur J Pediatr 2009; 168: 1043–1048

central diabetes insipidus may serve as a marker of hypothalamic damage or dysfunction. Children who have hypothalamic tumor involvement have higher leptin levels than those without hypothalamic involvement (Table 2.5). Younger age at diagnosis is a risk factor unrelated to hypothalamic involvement; some authors argue that it is related to ongoing brain growth and myelinization until 4 years of age [28]. The dose of radiation (>51 Gy) is important for development of HyOb in older as well as younger children; it may be associated with cognitive dysfunction, fatigue, and attention deficits [28].

Multiple hormone deficiencies are common in craniopharyngioma, with frequencies ranging from 40 to 87% [24]. GH deficiency, hypothyroidism, hypogonadism, and hyperprolactinemia may contribute to weight gain in some patients (see Chap. 19 by Dr. Freemark on the Pathogenesis of Weight Gain in Endocrine and Metabolic Disorders). High-dose glucocorticoid treatment in the immediate postoperative period can exacerbate hyperphagia, but chronic replacement of hydrocortisone at physiologic replacement doses (5–8 mg/m^2/day) should not promote excess weight gain. As noted above, a recent study found diabetes insipidus to be an endocrine marker for HyOb risk [28, 35]. This may reflect disruption of the hypothalamic pituitary stalk and/or more severe hypothalamic damage or dysfunction. GH treatment of children with HyOb may reduce BMI in some cases. However, one study found that GH treatment had only a slight beneficial effect on the rate of gain in body weight [36].

Imaging studies indicate that the degree of obesity correlates with the degree and extent of hypothalamic damage. Reducing hypothalamic damage is therefore a major objective of neurosurgery. For unfavorably localized tumors, limited resection should be performed to preserve neural and vascular integrity and to avoid further damage to hypothalamic and optic structures [26]. Although there is no consensus about the optimal and standard therapeutic approach for pediatric craniopharyngioma, current strategies favor subtotal resection combined with postoperative adjuvant focal radiotherapy [24, 26]. Elowe-Gruau and colleagues found that this approach reduced the frequency of severe obesity and was associated with similar local recurrence rates when compared with complete resection [37]. Mallucci and colleagues suggested that comorbidities could be reduced in appropriate cases by drainage of tumor cysts followed by surgical resection [38]. In light of these findings, it seems that hypothalamus-sparing surgery combined with focal radiotherapy may limit the prevalence and severity of postoperative HyOb.

Mortality in Hypothalamic Obesity

As a well-known cause of HyOb, craniopharyngioma has the highest mortality rate in cases of tumors in the sellar region. The standardized mortality ratio in childhood-onset craniopharyngioma is 17 (95% Cl 6.3–37), which is higher

than observed in both adult-onset craniopharyngioma and other childhood central nervous system malignancies [39]. Increases in BMI-SDS >1 SDS after 6 months of tumor therapy are associated with higher mortality rates [27].

The causes of mortality in adults with HyOb include hypothalamic insufficiency (ACTH and ADH deficiencies), cardiovascular disease, myocardial infarction, type 2 diabetes mellitus, cerebrovascular disease, and sleep apnea [39]. In children, obstructive sleep apnea and central sleep apnea seem to be the predominant causes of death [27]. However, decreased sympathetic nervous system activity and increased parasympathetic nervous system activity play important roles: cardiac arrhythmias and severe sleep-disordered breathing (SDB) may increase the risk of sudden death [27]. The treatment of SDB requires a multidisciplinary approach involving a pediatric sleep physician, pediatric endocrinologist, exercise physiologist, and otolaryngologist. An evaluation for SDB via polysomnography should be performed during the early stages of HyOb, and noninvasive ventilation begun in those affected as soon as possible.

Treatment

We now have a greater understanding of the pathways regulating appetite and satiety and the mechanisms of HyOb development, yet there is still no curative therapy for HyOb. As in simple "exogenous" obesity, the first-line treatment is lifestyle modification. HyOb is often unresponsive to diet and exercise, but patients should be encouraged to adopt a healthy diet and to maintain regular physical activity to the extent possible. A multidisciplinary approach involving the parents and school may assist the child in controlling weight gain. Rakhshani and colleagues compared a comprehensive care clinic (CCC) model, which includes medical, behavioral, dietary, and exercise support and with a standard care model in post-op children with brain tumors. They found that percent weight gain, percent of ideal body weight, and increment in BMI were lower in the CCC model; children also reported improved quality of life, physical functioning, and school performance [40].

Pharmacological Treatment

Patients with HyOb have impaired sympathoadrenal activation, so treatment with sympathomimetic agents has been recommended to decrease weight gain. The use of dextroamphetamine in five children with HyOb following surgery for craniopharyngioma reduced the rate of weight gain and stabilized BMI during a 24-month treatment protocol. Caloric intake did not change during treatment, but spontaneous physical activity increased significantly [34]. Another study showed similar effects, with weight stabilization and improvements in daytime wakefulness observed in 12 hypothalamic obese children treated with dextroamphetamine [41]. Additionally, caffeine and ephedrine administration in three children with HyOb resulted in weight loss in two of them [42]. Larger studies of efficacy are needed before suggesting dextroamphetamine for HyOb treatment. Moreover, chronic sympathomimetic therapy can increase heart rate and blood pressure and may thereby increase long-term cardiovascular risk.

Parasympathetic hyperactivity causes hyperinsulinemia, which has a critical role in weight gain associated with hypothalamic disease. Hence, inhibition of insulin secretion with somatostatin analogs was attempted as a means for treating HyOb. In a double-blind, randomized controlled study, octreotide caused significant reduction in weight gain in children with HyOb due to brain tumors or radiotherapy [43]. However, a larger multinational study with octreotide-LAR in 60 patients with HyOb was terminated because of ineffectiveness in reducing BMI [44]. In addition, serious side effects including gallstones, abdominal discomfort, and flatulence were reported in these studies [43, 44]. A pilot study treating adolescents with HyOb with a combination of diazoxide (which inhibits insulin secretion) and metformin showed reductions in weight gain and BMI [45]. However, a follow-up placebo-controlled investigation found that

diazoxide alone had no effect on weight gain after 2 months of treatment [46].

Decreased sympathetic nervous system activation and a possible reduction in type 2 deiodinase activity in HyOb [47] have stimulated interest in clinical trials using triiodothyronine (T3). In three patients, significant weight loss was reported with no symptoms of hyperthyroidism [47]. Inhibitors of 11β-HSD1 are potential therapeutic agents, but their use has not yet been explored.

A possible alternative approach could entail the use of analogs of glucagon-like peptide-1 (GLP-1). GLP-1 reduces food intake and body weight via direct effects in arcuate nucleus [6]. In a recent study, the GLP-1 analog liraglutide 3.0 mg caused loss of more than 10% of body weight in one-third of 3731 obese adults; however, adverse events (nausea, vomiting, diarrhea) were common, and gallbladder disease and/or pancreatitis occurred in 6.2% of the patients [48]. Zoicas and coworkers used a GLP-1 analog in nine (eight exenatide, one liraglutide) adult patients with HyOb; eight also had T2DM. Although one patient withdrew quickly because of intolerable nausea and vomiting, there was substantial weight loss in the remaining eight patients (−13.1 ± 5.1 kg (range −9 to −22). Insulin resistance and HbA1c levels also improved [49]. Substantial and sustained weight loss with exenatide or liraglutide was observed in other cases of HyOb (one patient was 17 years old), with no severe side effects [50, 51]. Additional trials seem warranted.

Although an effect of melatonin on weight gain in humans with HyOb has not yet been demonstrated, studies in rats observed that administration of a melatonin agonist (NEU-P11) or a MT1/MT2 receptor agonist (ramelteon) decreased body weight and increased insulin sensitivity in rats [52, 53]. These studies suggest potential new options for treatment of HyOb.

Finally, a recent study showed that a pharmacologic agonist (setmelanotide) for the melanocortin 4 receptor (MCR4) reversed hyperphagia and caused impressive weight loss (51 kg after 42 weeks and 20.5 kg after 12 weeks) in two patients with mutations in POMC [54]. Whether or not MCR4 agonists would reduce body weight in patients with postsurgical HyOb is currently unclear.

Surgical Treatment

Bariatric surgery has proved effective in the treatment of patients with severe obesity and comorbidities. The number of adolescent patients who have undergone bariatric surgery is increasing, and the outcomes thus far are comparable or better than those seen in adults [55, 56].

As recommended by the ASMBS (American Society for Metabolic and Bariatric Surgery) pediatric guidelines in 2012, the selection criteria for bariatric procedures in adolescents should include a BMI ≥35 kg/m^2 with major comorbidities (type 2 diabetes mellitus, moderate to severe sleep apnea, pseudotumor cerebri, or severe nonalcoholic steatohepatitis) or a BMI ≥40 kg/m^2 with other comorbidities (hypertension, insulin resistance, glucose intolerance, substantially impaired quality of life or activities of daily living, dyslipidemia, and mild sleep apnea) [55]. Furthermore, the teenager should have completed or nearly completed skeletal and sexual developmental (95% of linear growth or Tanner IV). Nevertheless, the severity of the weight gain in HyOb places even a young teenager at risk of life-threatening complications that may outweigh the theoretical risk of growth impairment following surgery [56].

There is as yet no randomized controlled study of bariatric surgery in adolescents with postsurgical HyOb and very limited experience with surgical procedures in the prepubertal period. On the other hand, a recent study demonstrated significant weight loss in 24 children (4.9–18 years, mean age 10.7) with Prader-Willi syndrome who underwent laparoscopic sleeve gastrectomy. Patients lost 14.7% (n = 22) and 10.7% (n = 7) of body weight by the first and fifth annual visits, respectively; 95% of comorbidities remitted or improved with no postoperative complications [57]. A meta-analysis of the effects of bariatric surgery in postsurgical adolescents and adults with craniopharyngioma found net weight loss of

6.1% after 12 months ($n = 6$) in the group receiving adjustable gastric bands, 20.2% ($n = 6$) in the group undergoing Roux-en-Y gastric bypass, 19.6% ($n = 8$) in the patients subjected to vertical sleeve gastrectomy, and 24.8% in the single patient undergoing biliopancreatic diversion. Long-term studies are needed to define appropriate selection criteria and the optimal procedure(s) for bariatric surgery in HyOb [58].

Conclusion

Hypothalamic obesity (HyOb) is a complex neuroendocrine disorder caused by damage to the hypothalamus, which results in disruption of energy regulation. This devastating problem can have profound effects on morbidity and mortality. Conventional lifestyle modification usually fails, and there is at present no curative pharmacologic treatment. Although several agents have been used to treat HyOb, the results are inconclusive and generally unsatisfactory. Thus, the clinician should be alert and vigilant in patients at risk for development of HyOb; prevention and management of HyOb should begin before neurosurgery and should provide an intensive and comprehensive multidisciplinary approach when weight gain begins.

Editor's Comments and Questions

1. Hypothalamic obesity is an intractable problem resulting from defects in α-MSH signaling, central resistance to the actions of leptin and insulin, vagal hyperactivity, glucocorticoid therapy, and reductions in resting and physical activity energy expenditure. Untreated GH deficiency, central hypothyroidism, hypogonadism, and hyperprolactinemia may exacerbate weight gain in postsurgical patients.

   Once established, severe adiposity is difficult or impossible to reverse without bariatric surgery. Ideally this might be avoided if excess weight gain could be prevented. I generally warn families from the outset about the risks for hypothalamic obesity and suggest that they begin to limit the child's intake of sugary drinks, fast foods, and starches even *before* tumor resection. I also consider pharmacologic intervention *prior to* obvious weight gain in those at high risk, as defined by the size and locale of the lesion, the surgical outcome, and the feeding behavior in the postoperative period. For that purpose I have used metformin, with variable (and somewhat limited) success. I do not begin pharmacotherapy prior to hospital discharge and strongly encourage ongoing compliance with dietary restriction. What are your thoughts about this approach?

2. While initial responses to GLP-1 analogs are promising, their use may be problematic in perioperative patients treated with high-dose glucocorticoids, which can exacerbate gastritis and potentiate the risks of pancreatitis[a]. The initial response to setmelanotide was dramatic in two adults with POMC mutations[b]. In theory, postsurgical patients with hypothalamic obesity would fail to respond to MCR4 agonists because of structural damage to α-MSH-responsive centers. However, there might be gradations of hypothalamic damage and dysfunction among children undergoing hypothalamic surgery, such that some response to agonist might be retained in some patients. This possibility awaits formal investigation; nevertheless, do you agree with the general concept?

Authors' Responses

1. We completely agree with you. From the beginning, families should be informed about the risk of development of HyOb and the changing of eating

habits before operation. Also, frequent visits after hospital discharge are necessary especially for the first year. For prophylactic pharmacotherapy, we think that we need controlled studies for recommendation of this kind of treatment.

2. Yes. We agree with the general concept. Although GLP-1 analogs seem to be a good option for HyOb patients, their side effects cannot be ignored. So they might be used in selected patients who are not in the perioperative period and are stable in terms of hormone replacement. We also think that setmelanotide deserves a trial.

References for Editor's Comments and Questions Section

(a) Freemark M. Liraglutide in Weight Management. N Engl J Med. 2015;373(17):1780–1.
(b) Kühnen P, Clément K, Wiegand S, Blankenstein O, Gottesdiener K, Martini LL, Mai K, Blume-Peytavi U, Grüters A, Krude H. Proopiomelanocortin Deficiency Treated with a Melanocortin-4 Receptor Agonist. N Engl J Med. 2016; 375(2):240–6.

References

1. King BM. The rise, fall, and resurrection of the ventromedial hypothalamus in the regulation of feeding behavior and body weight. Physiol Behav. 2006;87:221–44.
2. Haliloglu B, Bereket A. Hypothalamic obesity in children: pathophysiology to clinical management. J Pediatr Endocrinol Metab. 2015;28(5–6):503–13.
3. Bereket A, Kiess W, Lustig RH, Muller HL, Goldstone AP, Weiss R, et al. Hypothalamic obesity in children. Obes Rev. 2012;13(9):780–98.
4. Wardlaw SL. Hypothalamic proopiomelanocortin processing and the regulation of energy balance. Eur J Pharmacol. 2011;6660(1):213–9.
5. Cowley MA, Smith RG, Diano S, Tschöp M, Pronchuk N, Grove KL, Strasburger CJ, Bidlingmaier M, Esterman M, Heiman ML, Garcia-Segura LM, Nillni EA, Mendez P, Low MJ, Sotonyi P, Friedman JM, Liu H, Pinto S, Colmers WF, Cone RD, Horvath TL. The distribution and mechanism of action of ghrelin in the CNS demonstrates a novel hypothalamic circuit regulating energy homeostasis. Neuron. 2003;37(4):649–61.
6. Woods SC, D'Alessio DA. Central control of body weight and appetite. J Clin Endocrinol Metab. 2008;93(11 Suppl 1):S37–50.
7. Maekawa F, Fujiwara K, Toriya M, Maejima Y, Nishio T, Toyoda Y, Nohara K, Yashiro T, Yada T. Brain-derived neurotrophic factor in VMH as the causal factor for and therapeutic tool to treat visceral adiposity and hyperleptinemia in type 2 diabetic Goto-Kakizaki rats. Front Synaptic Neurosci. 2013;5:7.
8. Lee M, Korner J. Review of physiology, clinical manifestations, and management of hypothalamic obesity in humans. Pituitary. 2009;12(2):87–95.
9. Sakurai T. Roles of orexins in the regulation of body weight homeostasis. Obes Res Clin Pract. 2014;8(5):e414–20.
10. Lustig RH. Autonomic dysfunction of the β-cell and the pathogenesis of obesity. Rev Endocr Metab Disease. 2003;4:23–32.
11. Guran T, Turan S, Bereket A, et al. The role of leptin, soluble leptin receptor, resistin, and insulin secretory dynamics in the pathogenesis of hypothalamic obesity in children. Eur J Pediatr. 2009;168:1043–8.
12. Bray GA, Inoue S, Nishizawa Y. Hypothalamic obesity. The autonomic hypothesis and the lateral hypothalamus. Diabetologia. 1981;20(Suppl):366–77.
13. Simoneau-Roy J, O'Gorman C, Pencharz P, Adeli K, Daneman D, Hamilton J. Insulin sensitivity and secretion in children and adolescents with hypothalamic obesity following treatment for craniopharyngioma. Clin Endocrinol. 2010;72(3):364–70.
14. Lustig RH. Hypothalamic obesity: causes, consequences, treatment. Pediatr Endocrinol Rev. 2008;6(2):220–7.
15. Shaikh MG, Grundy R, Kirk J. Hyperleptinaemia rather than fasting hyperinsulinaemia is associated with obesity following hypothalamic damage in children. Eur J Endocrinol. 2008;159(6):791–7.
16. Bucher H, Zapf J, Torresani T, Prader A, Froesch ER, Illig R. Insulin-like growth factors I and II, prolactin, and insulin in 19 growth hormone deficient children with excessive, normal, or decreased longitudinal growth after operation for craniopharyngioma. N Engl J Med. 1983;309:1142–6.
17. Roth CL, Hunneman DH, Gebhardt U, Stoffel-Wagner B, Reinehr T, Muller HL. Reduced sympathetic metabolites in urine of obese patients with craniopharyngioma. Pediatr Res. 2007;61:496–501.
18. Wang C, Billington CJ, Levine AS, Kotz CM. Effect of CART in the hypothalamic paraventricular nucleus on feeding and uncoupling protein gene expression. Neuroreport. 2000;11:3251–5.
19. Müller HL, Handwerker G, Wollny B, Faldum A, Sorensen N. Melatonin secretion and increased daytime sleepiness in childhood craniopharyngioma patients. J Clin Endocrinol Metab. 2002;87:3993–6.

20. Wolden-Hanson T, Mitton DR, McCants RI, Yellon SM, Wilkinson CW, Matsumoto AM, et al. Daily melatonin administration to middle aged male rats suppresses body weight, intra abdominal adiposity, and plasma leptin, and insulin independent of food intake and total body fat. Endocrinology. 2000;141:487–97.
21. Kassayova M, Markova M, Bojkova B, Adamekova E, Kubartka P, Ahlersova E, et al. Influence of long-term melatonin administration on basic physiological and metabolic variables of young Wistar Han rats. Biologia. 2006;61:313–20.
22. Tiosano D, Eisentein I, Militianu D, Chrousos GP, Hochberg Z. 11 beta-Hydroxysteroid dehydrogenase activity in hypothalamic obesity. J Clin Endocrinol Metab. 2003;88:379–84.
23. Friedberg M, Zoumakis E, Hiroi N, Bader T, Chrousos GP, Hochberg Z. Modulation of 11 beta-hydroxysteroid dehydrogenase type 1 in mature human subcutaneous adipocytes by hypothalamic messengers. J Clin Endocrinol Metab. 2003;88:385–93.
24. Müller HL. Craniopharyngioma. Endocr Rev. 2014;35(3):513–43.
25. Müller HL, Bueb K, Bartels U, et al. Obesity after childhood craniopharyngioma–German multicenter study on pre-operative risk factors and quality of life. Klin Padiatr. 2001;213:244–9.
26. Müller HL. Craniopharyngioma and hypothalamic injury: latest insights into consequent eating disorders and obesity. Curr Opin Endocrinol Diabetes Obes. 2016;23:81–9.
27. Haliloglu B, Atay Z, Guran T, Abalı S, Bas S, Turan S, Bereket A. Risk factors for mortality caused by hypothalamic obesity in children with hypothalamic tumours. Pediatr Obes. 2016;11(5):383–8.
28. Lustig RH, Post SM, Srivannaboon K, Rose SR, Danish RK, Burghen GA, et al. Risk factors for the development of obesity in children surviving brain tumors. J Clin Endocrinol Metab. 2003;88:611–6.
29. Iughetti L, Bruzzi P, Predieri B, Paolucci P. Obesity in patients with acute lymphoblastic leukemia in childhood. Ital J Pediatr. 2012;38:4.
30. Srinivasan S, Ogle GD, Garnett SP, Briody JN, Lee JW, Cowell CT. Features of the metabolic syndrome after childhood craniopharyngioma. J Clin Endocrinol Metab. 2004;89:81–6.
31. Hoffmann A, Bootsveld K, Gebhardt U, Daubenbüchel AM, Sterkenburg AS, Müller HL. Nonalcoholic fatty liver disease and fatigue in long-term survivors of childhood-onset craniopharyngioma. Eur J Endocrinol. 2015;173(3):389–97.
32. Müller HL, Handwerker G, Gebhardt U, et al. Melatonin treatment in obese patients with childhood craniopharyngioma and increased daytime sleepiness. Cancer Causes Control. 2006;17:583–9.
33. Rosen G, Brand SR. Sleep in children with cancer: case review of 70 children evaluated in a comprehensive pediatric sleep center. Support Care Cancer. 2011;19(7):985–94.
34. Mason PW, Krawiecki N, Meacham LR. The use of dextroamphetamine to treat obesity and hyperphagia in children treated for craniopharyngioma. Arch Pediatr Adolesc Med. 2002;156:887–92.
35. Roth CL, Eslamy H, Werny D, Elfers C, Shaffer ML, Pihoker C, Ojemann J, Dobyns WB. Semiquantitative analysis of hypothalamic damage on MRI predicts risk for hypothalamic obesity. Obesity (Silver Spring). 2015;23(6):1226–33.
36. Geffner M, Lundberg M, Koltowska-Häggström M, Abs R, Verhelst J, Erfurth EM, et al. Changes in height, weight, and body mass index in children with craniopharyngioma after three years of growth hormone therapy: analysis of KIGS (Pfizer international growth database). J Clin Endocrinol Metab. 2004;89(11):5435–40.
37. Elowe-Gruau E, Beltrand J, Brauner R, et al. Childhood craniopharyngioma: hypothalamus-sparing surgery decreases the risk of obesity. J Clin Endocrinol Metab. 2013;98:2376–82.
38. Mallucci C, Pizer B, Blair J, et al. Management of craniopharyngioma: the Liverpool experience following the introduction of the CCLG guidelines. Introducing a new risk assessment grading system. Childs Nerv Syst. 2012;28:1181–92.
39. Olsson DS, Andersson E, Bryngelsson IL, Nilsson AG, Johannsson G. Excess mortality and morbidity in patients with craniopharyngioma, especially in patients with childhood onset: a population-based study in Sweden. J Clin Endocrinol Metab. 2015;100(2):467–74.
40. Rakhshani N, Jeffery AS, Schulte F, Barrera M, Atenafu EG, Hamilton JK. Evaluation of a comprehensive care clinic model for children with brain tumor and risk for hypothalamic obesity. Obesity. 2010;18(9):1768–74.
41. Ismail D, O'Connell MA, Zacharin MR. Dexamphetamine use for management of obesity and hypersomnolence following hypothalamic injury. J Pediatr Endocrinol Metab. 2006;19:129–34.
42. Greenway FL, Bray GA. Treatment of hypothalamic obesity with caffeine and ephedrine. Endocr Pract. 2008;14:697–703.
43. Lustig RH, Hinds PS, Ringwald-Smith K, et al. Octreotide therapy of pediatric hypothalamic obesity: a double-blind, placebo-controlled trial. J Clin Endocrinol Metab. 2003;88:2586–92.
44. Weiss R.. URL http://clinicaltrials.gov/ct2/show/NCT00076362.
45. Hamilton JK, Conwell LS, Syme C, Ahmet A, Jeffery A, Daneman D. Hypothalamic obesity following Craniopharyngioma surgery: results of a pilot trial of combined Diazoxide and metformin therapy. Int J Pediatr Endocrinol. 2011;2011:417949.
46. Brauner R, Serreau R, Souberbielle JC, Pouillot M, Grouazel S, Recasens C, Zerah M, Sainte-Rose C, Treluyer JM. Diazoxide in children with obesity after hypothalamic-pituitary lesions: a randomized, placebo-controlled trial. J Clin Endocrinol Metab. 2016;101(12):4825–33.
47. Fernandes JK, Klein MJ, Ater JL, Kuttesch JF, Vassilopoulou-Sellin R. Triiodothyronine supple-

mentation for hypothalamic obesity. Metabolism. 2002;51:1381–3.
48. Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, Krempf M, Lau DC, le Roux CW, Violante Ortiz R, Jensen CB, Wilding JP, SCALE Obesity and Prediabetes NN8022-1839 Study Group. A randomized, controlled trial of 3.0 mg of Liraglutide in weight management. N Engl J Med. 2015;373(1):11–22.
49. Zoicas F, Droste M, Mayr B, Buchfelder M, Schöfl C. GLP-1 analogues as a new treatment option for hypothalamic obesity in adults: report of nine cases. Eur J Endocrinol. 2013;168(5):699–706.
50. Simmons JH, Shoemaker AH, Roth CL. Treatment with glucagon-like Peptide-1 agonist exendin-4 in a patient with hypothalamic obesity secondary to intracranial tumor. Horm Res Paediatr. 2012;78(1):54–8.
51. Ando T, Haraguchi A, Matsunaga T, Natsuda S, Yamasaki H, Usa T, Kawakami A. Liraglutide as a potentially useful agent for regulating appetite in diabetic patients with hypothalamic hyperphagia and obesity. Intern Med. 2014;53(16):1791–5.
52. She M, Deng X, Guo Z, Laudon M, Hu Z, Liao D, et al. NEU-P11, a novel melatonin agonist, inhibits weight gain and improves insulin sensitivity in high-fat/high-sucrose-fed rats. Pharmacol Res. 2009;59:248–53.
53. Oxenkrug GF, Summergrad P. Ramelteon attenuates age-associated hypertension and weight gain in spontaneously hypertensive rats. Ann N Y Acad Sci. 2010;1199:114–20.
54. Kühnen P, Clément K, Wiegand S, Blankenstein O, Gottesdiener K, Martini LL, Mai K, Blume-Peytavi U, Grüters A, Krude H. Proopiomelanocortin deficiency treated with a Melanocortin-4 receptor agonist. N Engl J Med. 2016;375(3):240–6.
55. Michalsky M, Reichard K, Inge T, Pratt J. Lenders C; American Society for Metabolic and Bariatric Surgery. ASMBS pediatric committee best practice guidelines. Surg Obes Relat Dis. 2012;8(1):1–7.
56. Desai NK, Wulkan ML, Inge TH. Update on adolescent bariatric surgery. Endocrinol Metab Clin N Am. 2016;45(3):667–76.
57. Alqahtani AR, Elahmedi MO, Al Qahtani AR, Lee J, Butler MG. Laparoscopic sleeve gastrectomy in children and adolescents with Prader-Willi syndrome: a matched-control study. Surg Obes Relat Dis. 2016;12(1):100–10.
58. Bretault M, Boillot A, Muzard L, et al. Clinical review: bariatric surgery following treatment for craniopharyngioma: a systematic review and individual-level data meta-analysis. J Clin Endocrinol Metab. 2013;98:2239–46.