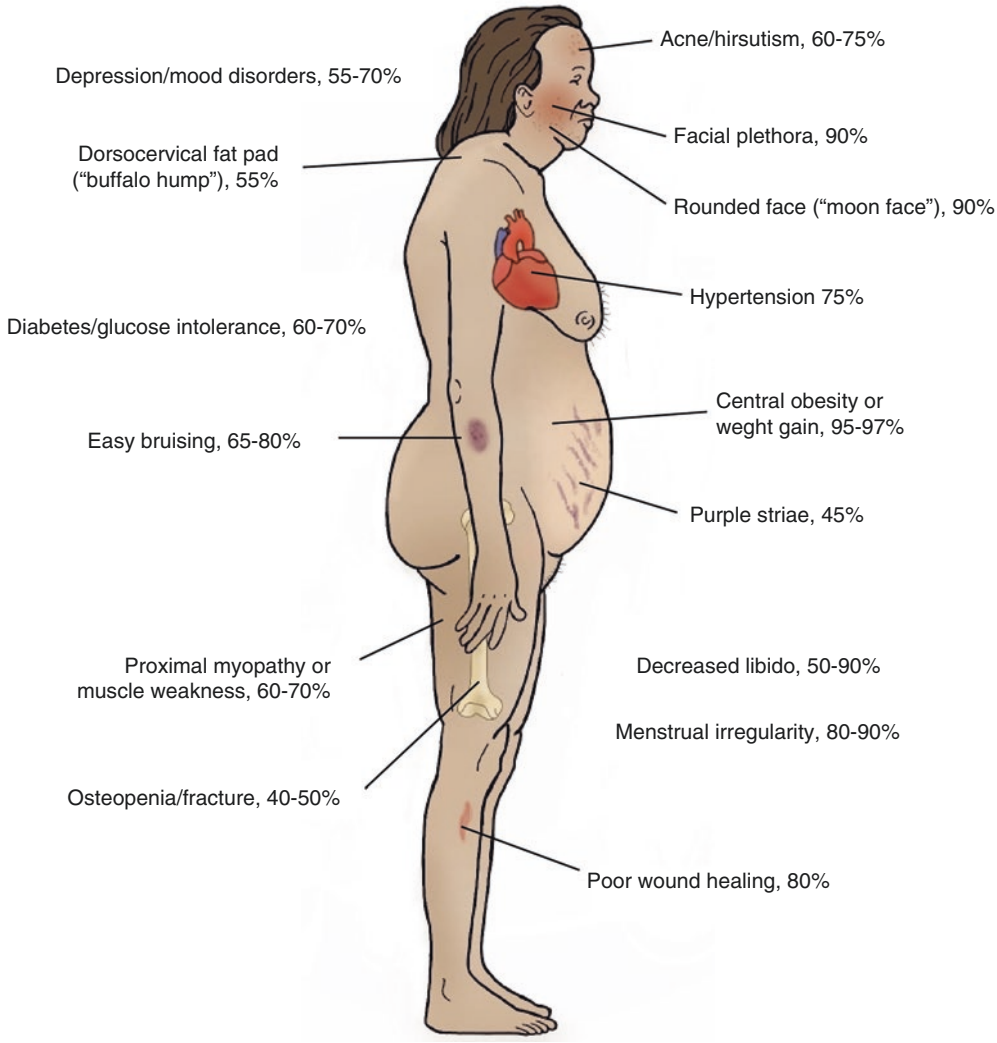

Fig. 10.4 Clinical features of Cushing's syndrome and their prevalence. (Modified from Newell-Price et al. [26], Ceccato and Boscaro [32], Boscaro and Arnaldi [33], Nieman et al. [34], Lonser et al. [35])

osteoporosis, susceptibility to infection, cardiac disease, and hypercoagulability [36]. Accordingly, patients with Cushing's syndrome have a remarkably increased cardiovascular risk. Mancini et al. estimated that 80% of Cushing's syndrome patients have a >20% risk of a major cardiovascular event within the next 10 years [40]. This partly explains the significant morbidity and mortality associated with Cushing's syndrome [41]: the mortality rate in patients with Cushing's syndrome is estimated to be four times higher than expected in a control population [38], with approximately 71.4% of deaths attributed to cardiovascular causes or infection [41].

Early diagnosis is important to mitigate the effects of Cushing's syndrome on patient quality of life [42]; however, most of the signs and symptoms of Cushing's syndrome are commonly

found in the general population. As a result, mild disease may be subclinical, and identifying patients to be screened for Cushing's syndrome requires an extensive history [43]. More definitive guidelines for which populations should be screened for Cushing's syndrome may help make the diagnosis more efficient. For example, León-Justel et al. developed a risk scoring system in which patients with two of five nonspecific features including hypertension, uncontrolled diabetes, obesity, osteoporosis, and virilization syndrome were screened for Cushing's syndrome. They found an increased prevalence (7.4%) of Cushing's syndrome in this population [44]. Thus, scoring systems like this could improve the identification of at-risk patients to be screened for Cushing's syndrome.

Diagnosis

After exogenous glucocorticoid exposure is excluded, the Endocrine Society's Clinical Practice Guidelines recommend the following biochemical screening tests be used to establish the diagnosis of Cushing's syndrome: the overnight dexamethasone suppression test, 24-hour urine free cortisol, and midnight salivary cortisol levels. Two of three positive results indicate a diagnosis of Cushing's syndrome [34].

Table 10.2 compares the various biochemical screening tests used in the diagnosis of Cushing's syndrome [32, 34, 45–50]. Firstly, the overnight dexamethasone suppression test examines whether negative feedback inhibition of glucocorticoids on the hypothalamus-pituitary-adrenal (HPA) axis is normal. Administration of dexamethasone, a potent glucocorticoid, normally results in suppression of ACTH and cortisol secretion. There is a failure of suppression in endogenous Cushing's syndrome [51]. To perform the test, 1 mg of dexamethasone is given orally between 11 PM and midnight. The serum cortisol level is measured the following morning between 8 and 9 AM. Generally, the results are considered normal if the cortisol is suppressed below 1.8 μg/dL (50 nmol/liter), whereas higher values are associated with Cushing's syndrome [52]. This test yields a sensitivity of >95% and specificity of 80–85% [34, 45]. However, the absorption and metabolism of dexamethasone may vary between patients and influence the results. Drugs that induce the enzymatic activity of CYP3A4 (e.g., phenytoin and carbamazepine) may reduce dexamethasone concentrations producing false positives, whereas clearance of dexamethasone may be reduced in patients with liver or renal disease to produce false negatives. Hence, it is important to check the patient's dexamethasone level. Additionally, false positives are seen in 50% of women taking oral contraceptive pills (OCPs) due to increased cortisol-binding globulin (CBG), falsely elevating total cortisol levels [34, 53]. Therefore, the overnight dexamethasone suppression test should not be used in patients on OCPs.

The urine free cortisol (UFC) test offers an integrated assessment of cortisol secretion over 24 hours. Unlike serum cortisol, UFC measures unbound cortisol in the urine and is therefore unaffected by conditions and medications that alter the concentration of CBG. This method involves the patient collecting and refrigerating their urine over 24 hours, discarding the first morning void so collection begins with an empty bladder. In most assays, the upper normal limit ranges between 220 and 330 nmol/24 h. Raised levels of cortisol secretion are consistent with Cushing's syndrome [51]. However, it is recommended at least two collections are performed because of high UFC variability in Cushing's syndrome patients. Petersenn et al. estimated the intrapatient variability to be approximately 50% in UFC measurements among patients with Cushing's syndrome. Evaluating more than two 24-hour collections failed to decrease the variability [54]. The estimated sensitivity and specificity of UFC are 70–75% and 40–90%, respectively [34, 45]. False positives may result from high fluid intake or GC use during the collection, while false negatives may occur in patients with a decreased glomerular filtration rate (GFR) [34].

Table 10.2 Biochemical screening tests for the diagnosis of Cushing's syndrome

Test	Basis	Technique	Sensitivity	Specificity	Advantages	Disadvantages
Dexamethasone suppression test	ACTH-secreting tumors lose sensitivity to glucocorticoid negative feedback	1 mg dexamethasone at 11 PM, measure cortisol between 8 and 9 AM	>95%	80–85%	Subclinical Cushing's syndrome	Decreased dexamethasone absorption
						Increased CBG (oral contraceptives)
						Altered dexamethasone metabolism/ clearance (P450 enzyme system interactions, liver or renal disease)
						Pseudo-Cushing's
Late-night salivary cortisol	Measures the disruption of the normal circadian rhythm	Salivary sample between 11 PM and midnight	90–98%	90–100%	In-home collection	Smoking/chewing tobacco
					Detecting mild or cyclic Cushing's syndrome	Exogenous steroids
						Abnormal sleep-wake cycles
					Renal failure	Salivary cortisol increases with age, HTN, diabetes
24-hour urine free cortisol (UFC)	Measures cortisol secretion	Urine collected over 24 hours, discarding the first void	70–75%	40–90%	Integrated tissue exposure to free cortisol	Improper collection
						Intrapatient variability
					Measures cortisol not bound to CBG	High fluid intake >5 L
					Pregnancy and OCPs	Contamination
						Renal insufficiency
						Pseudo-Cushing's syndrome
Desmopressin (DDAVP) stimulation	Measures desmopressin-stimulated ACTH secretion in corticotroph adenomas	Plasma ACTH and serum cortisol levels measured before and after 10 μg intravenous DDAVP administration	75–90%	90–92%	Pseudo-Cushing's syndrome	Variability in ACTH assays
					Early indicator of recurrent Cushing's disease	Lack of normative data
Dexamethasone-CRH test	Measures cortisol secretion in response to CRH after dexamethasone suppression	Eight doses of 0.5 mg dexamethasone given orally over several days prior to morning administration of CRH, followed by plasma ACTH and cortisol measures	88–100%	50–100%	Pseudo-Cushing's syndrome	Expensive
						Altered dexamethasone metabolism
Hair cortisol	Measures historical cortisol exposure	Proximal 1–3 cm hair sample collected from vertex of scalp, hair cortisol quantified with enzyme immunoassay kits	86–93%	90–98%	Retrospective marker of long-term exposure	Human hair growth rate varies between individuals
					Noninvasive collection	Unclear effects of artificial hair dye, environmental exposures, race and ethnicity
Dehydro-epiandrosterone sulfate (DHEAS)	Regulated by ACTH, DHEAS is a marker for ACTH levels	Single basal measure of DHEAS	68–100%	75–92%	Prolonged half-life in serum and more stable levels compared to ACTH	Preexisting ACTH suppression
						Data is inadequate
					Subclinical Cushing's syndrome	
					Adrenal incidentalomas	

Modified from Nieman et al. [34], Bansal et al. [45], Ceccato and Boscaro [32], Nieman et al. [46], Findling and Raff [47], Thomson et al. [48], Greene et al. [49], Dennedy et al. [50]

Lastly, measuring the midnight salivary cortisol level is an effective and efficient test to aid in the diagnosis of Cushing's syndrome. In normal individuals, cortisol levels follow a diurnal circadian cycle reaching a nadir around midnight [55]. In contrast, absence of a normal nadir at night is consistently seen in patients with Cushing's syndrome [56]. In practice, most providers ask their patients to collect a saliva sample on two separate evenings between 11 PM and midnight. Normal individuals typically have a cortisol level less than 125 ng/dl (4 nmol/liter) during the nadir [34]. A higher, positive result has a 90–98% sensitivity and 90–100% specificity for the diagnosis of Cushing's syndrome [34, 45]. Patients who smoke or use chewing tobacco may have false positives. False positives can also occur with direct contamination of the saliva with steroids and in patients with abnormal sleep-wake cycles or those experiencing excess stress before collection [34].

Ultimately, there are limitations to each of the current diagnostic tests, but new diagnostic modalities are emerging. For instance, measuring hair cortisol level has been proposed as a method to retrospectively obtain historical information on systemic cortisol exposure. Thomson et al. collected 1 cm hair sections and compared hair cortisol levels between Cushing's syndrome patients and controls. Hair cortisol levels were higher in patients with Cushing's syndrome and provided information for up to 18 months before the time of the sample [48]. Face classification software may also help to discriminate patients with Cushing's syndrome. A study by Kosilek et al. showed that facial analysis was able to correctly classify 85% of patients with Cushing's syndrome and 95% of controls, giving a testing accuracy comparable to screening tests currently used [57].

Pseudo-Cushing's Syndrome

When making the diagnosis, it is important to differentiate Cushing's syndrome from "pseudo-Cushing's syndrome." Pseudo-Cushing's syndrome refers to physiological, nonneoplastic states of hypercortisolism and is associated with neuropsychiatric disorders such as depression, poorly controlled diabetes mellitus, renal failure, and alcoholism [58]. Most pseudo-Cushing's states are mediated through subtle activation of the HPA axis. Like endogenous Cushing's syndrome, patients have attenuated sensitivity to glucocorticoid negative feedback. Over time, small increases in cortisol summate to result in chronic hypercortisolism. Other disorders such as anorexia, intense chronic exercise, obstructive sleep apnea, and multiple sclerosis are also associated with hypercortisolism, though their phenotypes are rarely confused with endogenous Cushing's syndrome [47].

Pseudo-Cushing's syndrome may produce clinical and biochemical findings suggestive of Cushing's syndrome, proving the distinction to be extremely difficult [59]. A detailed history and physical examination are the crucial first steps to making the distinction, with special attention given to alcohol intake and mental health. While there is no gold standard for differentiating the two clinical entities, most pseudo-Cushing's states will have mild cortisol excess and rarely have overt clinical manifestations of hypercortisolism [47]. Conversely, most patients with endogenous Cushing's syndrome have overt manifestations of hypercortisolism such as proximal myopathy, purple striae, easy bruising, hypertension, diabetes, hirsutism, and osteopenia [47, 58, 60]. Moreover, though false-positive results are possible, a normal late-night salivary cortisol and overnight dexamethasone suppression test makes the diagnosis of endogenous Cushing's syndrome extremely unlikely. In contrast, UFC has a poorer sensitivity for the detection of endogenous Cushing's syndrome, though marked elevations (3–4 times the upper limit) are suggestive. Repeated studies may be needed to make an accurate diagnosis in patients with high clinical suspicion [47].

Secondary tests such as desmopressin (DDAVP) stimulation and the dexamethasone-CRH test have been used to distinguish patients with endogenous Cushing's syndrome and pseudo-Cushing's states. The DDAVP stimulation test is typically performed in the morning, with plasma ACTH and serum cortisol levels measured before and after DDAVP administra-

tion. Because ACTH-secreting adenomas can express vasopressin receptors, administration of DDAVP stimulates ACTH secretion in patients with endogenous Cushing's syndrome and results in only a small or absent response in pseudo-Cushing's patients [58]. With an ACTH level >6 pmol/L (>27 pg/mL) supporting a diagnosis of endogenous Cushing's syndrome, the test has an estimated sensitivity of 75–90% and specificity of 90–92% to distinguish endogenous Cushing's syndrome from pseudo-Cushing's states. Furthermore, to perform a dexamethasone-CRH test, eight doses of dexamethasone are given orally over several days prior to morning administration of CRH. After which, plasma ACTH and cortisol are measured. Serum cortisol >1.4 ug/dl (39 nmol/L) in response to CRH after dexamethasone suppression supports a diagnosis of endogenous Cushing's syndrome with an estimated sensitivity and specificity of 88–100% and 50–100%, respectively [47].

Differential Diagnosis

After pathological hypercortisolism is confirmed, the next step is to measure plasma ACTH concentration to differentiate ACTH-dependent and ACTH-independent Cushing's syndrome. In the setting of hypercortisolism, an elevated plasma ACTH concentration suggests ACTH-dependent Cushing's syndrome, whereas a suppressed plasma ACTH indicates ACTH-independent Cushing's syndrome [61]. However, it is imperative that clinicians know which ACTH assay is used in their practice: the immunometric assay currently used in most clinical laboratories, the Siemens ACTH Immulite assay [ACTH(Immulite)], is susceptible to interference by heterophile antibodies and hormone fragments or precursors. Interfering substances can lead to incorrectly elevated results, confounding the diagnosis of Cushing's syndrome and leading to unnecessary diagnostic procedures [49, 62]. The Roches Cobas assay [ACTH(Cobas)] has been suggested to resolve discrepancies in the ACTH(Immulite) assay and has been recommended as an alternate ACTH assay to be used in the diagnosis of Cushing's syndrome [49]. Lastly, measuring dehydroepiandrosterone sulfate (DHEAS), an adrenal androgen regulated by ACTH, may prove to be a more reliable marker than ACTH due to its longer half-life and relatively more stable levels. In patients with ACTH-independent, subclinical hypercortisolism, Dennedy et al. found that a single basal measure of DHEAS offers comparable sensitivity and greater specificity to diagnose Cushing's syndrome when compared to the dexamethasone suppression test [50].

An elevated ACTH level supports a diagnosis of ACTH-dependent Cushing's syndrome and is most commonly due to an ACTH-secreting pituitary adenoma. Hence, pituitary magnetic resonance imaging (MRI) should be performed in all patients with ACTH-dependent Cushing's syndrome [29]. Most clinicians will make the diagnosis of pituitary-dependent Cushing's syndrome if imaging reveals an isolated pituitary lesion ≥6 mm [26]. However, it is important to note that, because approximately 10% of the normal adult population has asymptomatic pituitary adenomas [63], MRI has little value in differentiating pituitary-dependent Cushing's syndrome from ectopic ACTH secretion. Moreover, up to 40% of patients with pituitary-dependent Cushing's syndrome will have normal pituitary MRI scans [64]. In cases of uncertainty, bilateral inferior petrosal sinus sampling (IPSS) is considered the most reliable method to distinguish pituitary and non-pituitary sources of ACTH secretion [26]. During the invasive procedure, ACTH levels are simultaneously obtained from the periphery and the venous drainage of the pituitary via a catheter placed in both inferior petrosal sinuses. The central ACTH levels from the petrosal sinuses are expected to be higher than the levels in peripheral blood in cases of ACTH-secreting pituitary adenomas [65]. Direct stimulation of ACTH secretion with CRH enhances the sensitivity of the procedure [66], though false negatives and the invasiveness of the procedure remain as potential drawbacks [26].

Management

The primary treatment objectives for Cushing's syndrome include normalization of cortisol levels, resolution of symptoms, and prevention or recovery of the coexistent comorbidities and complications. Frequently, this requires a multimodal treatment approach [67]. First-line therapy for pituitary-dependent Cushing's syndrome is selective surgical resection of the adenoma, typically by transsphenoidal route [68].

Remission

Postoperative remission is generally defined as morning serum cortisol levels <5 μg/dL (<138 nmol/L) within 7 days of the operation [46]. While hypocortisolism after transsphenoidal surgery has been shown to be a reliable prognostic factor for remission, the criteria used to define remission are heterogenous within the literature. Remission can be defined by clinical and/or biochemical factors, with morning serum cortisol level alone or combined with UFC measures being the most commonly used biochemical assays to determine remission [69]. Likely in part attributed to the heterogeneity in definitions of remission, the initial remission rate following transsphenoidal pituitary surgery is variable and is estimated to be between 42% and 90% [67, 70, 71]. Microadenomas (<10 mm maximum tumor diameter) are more common and are associated with higher rates of postoperative remission compared to macroadenomas (>10 mm) [72, 73]. Furthermore, postoperative morning serum cortisol nadir may serve as a predictor for surgical outcomes: a meta-analysis by Stroud et al. found that patients with a postoperative morning serum cortisol nadir <2 μg/dL were more likely to experience remission and less likely to have recurrence compared to patients with a nadir >2 μg/dL (remission rate 95 vs. 46%, recurrence rate 10 vs. 37%). Other factors identified by Stroud et al. to be associated with better remission rates are summarized in Fig. 10.5, including absence of cavernous sinus invasion and confirmation with histopathology [73].

Recurrence

Recurrence of Cushing's syndrome is frequently characterized by return of clinical symptoms and biochemical evidence of hypercortisolism, though there is no clearly established definition.

While there is no consensus on which biochemical tests should be used for a definitive recurrence diagnosis, late-night salivary cortisol is the first biochemical test to reveal abnormal results (followed by the overnight dexamethasone suppression test and UFC) and is a highly sensitive approach to detect surgical treatment failure (90–100%) [74]. Thus, periodic late-night salivary cortisol has been recommended as the first choice in assessing Cushing's syndrome recurrence [71, 74].

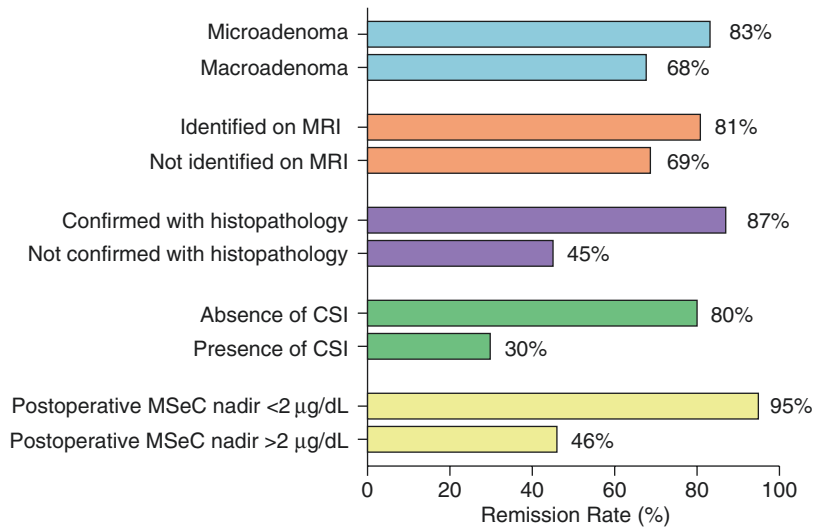

Fig. 10.5 Predictors of postoperative remission following primary transsphenoidal surgery for Cushing's disease. (Modified from Stroud et al. [73])
Abbreviations: *MRI* magnetic resonance imaging, *CSI* cavernous sinus invasion, *MSeC* morning serum cortisol

Reported recurrence rates range widely from 2% to 65% [71] and are generally higher in patients with macroadenomas [72, 73]. Prognostic factors associated with disease recurrence are largely unidentified; however, a meta-analysis by Roelfsema et al. found that microscopic tumor invasion, postoperative dexamethasone tests, and low basal postoperative cortisol concentrations are the factors most frequently reported to have a significant association with tumor recurrence in the relevant literature [75].

Disease persistence or recurrence may require repeat pituitary surgery, radiotherapy, bilateral adrenalectomy, or medical therapy [67]. Medical therapy can be directed at the level of the pituitary tumor, the adrenal glands, and the peripheral tissue. Dopamine agonists and somatostatin analogs can help normalize cortisol levels by inhibiting ACTH secretion [76, 77]. Other medical therapies for hypercortisolism include ketoconazole, which blocks several steps in the synthesis of cortisol in the adrenal cortex, and glucocorticoid receptor antagonists such as mifepristone [16]. A summary of the medical therapies used for pituitary-dependent Cushing's syndrome is summarized in Table 10.3 [78–81].

Repeat surgery and radiotherapy are recommended when there is evidence of residual tumor

Table 10.3 Drugs for the medical treatment of pituitary-dependent Cushing's syndrome

Drug	Dose	Overall response rate (%)	Toxicity
Pituitary-targeted drugs			
Cabergoline	0.5–6 mg weekly	32% (40–50% short term)	Hypotension, nausea, headache
Pasireotide*	s/c 600–900 mcg or i/m 10–30 mg monthly	18–26% (up to 50% with mild CD)	Hyperglycemia, GI, cholelithiasis, hyperglycemia
Roscovitine	400 mg twice daily	NA	Asthenia, nausea, vomiting, hypokalemia
Retinoic acid	80 mg once daily	NA	Mucositis, photosensitivity, hypertriglyceridemia
Gefitinib	250 mg once daily	NA	Skin reaction, diarrhea, pneumonitis
Silibinin	NA	NA	Unknown
Steroidogenesis inhibitors			
Ketoconazole	Starting 400, up to 1600 mg daily	54%	Hepatotoxicity, gastrointestinal symptoms, drug interactions, avoid proton pump inhibitors
Metyrapone	750–1000 mg in divided doses	60–75%	GI, hirsutism, hypertension, hypokalemia
Etomidate	0.1–0.2 mg/kg/hour	100% (short term)	ICU monitoring, sedative
Mitotane	1·5 g daily, increasing dose by 1·5 g every 24 h, up to a dose of 6 g	72–80%	GI, neurological side effects, drug interactions, hyperlipidemia, liver, gynecomastia
Osilodrostat (LCI699)*	10–60 mg/day	86%	GI, hirsutism, hypertension, hypokalemia
Levoketoconazole	400 mg daily	30%	NA
Glucocorticoid receptor antagonists			
Mifepristone*	300–1200 mg/day	50%	Abortifacient, fatigue, nausea, vomiting, hypertension, edema, endometrial thickening
Relacorilant	100–400 mg/day	NA	NA

*Drugs approved by the FDA for the treatment of pituitary-dependent Cushing's syndrome
Modified from Fleseriu and Petersenn [78], Ferriere et al. [79], Broersen et al. [80], Tritos and Biller [81]
Overall response rate represents that of the largest series. Drugs approved by the FDA for the treatment of pituitary-dependent Cushing's syndrome are indicated with an asterisk. Drugs without an asterisk are off-label or, if the overall response rate is indicated as NA, are currently in phase 2 or 3 clinical trials
Abbreviations: *NA* not applicable, *s/c* subcutaneous, *i/m* intramuscular, *CD* Cushing's disease, *GI* gastrointestinal symptoms

or concerns for mass effects or invasion. For radiotherapy, both stereotactic radiosurgery and fractionated radiotherapy result in similar rates of remission (43–58% and 46–84%, respectively). However, the major risk of radiotherapy is loss of pituitary function, occurring in 20–40% of patients at 10 years after radiation [35]. Bilateral adrenalectomy can be considered, typically after failure or intolerance of medical therapy; however, it is rarely performed for pituitary-dependent Cushing's syndrome and is only recommended as emergency treatment in patients with severe disease [34].

Postoperative Management

Hypocortisolism typically occurs after successful transsphenoidal surgery, with normal pituitary ACTH secretion inhibited from chronic cortisol exposure. Because resolution of normal ACTH and cortisol secretion frequently takes 6–12 months, patients receive glucocorticoid replacement during this period. Restoration of the normal HPA axis is monitored with morning cortisol levels and cortisol response to ACTH stimulation. Moreover, hypopituitarism can occur postoperatively. Hypogonadism, relative hypothyroidism, and low growth hormone similarly resolve over 6–12 months, though some patients may require treatment for ongoing endocrinological changes [35].

Furthermore, Cushing's syndrome patients have a greater risk of postoperative venous thromboembolism (VTE) compared to the general population due to activation of procoagulant factors and the coagulation cascade [82]. Estimated rates of VTE following surgery vary between 3.4% and 6% [82–86]. Thromboprophylaxis has been reported to significantly decrease the incidence of VTE in Cushing's syndrome patients. Boscaro et al. reported that 6% of Cushing's syndrome patients treated with unfractionated heparin daily for at least 2 weeks postoperatively developed VTE, whereas 20% of those untreated developed VTE [87]. However, there are currently no guidelines on thromboprophylaxis for patients with Cushing's syndrome before or after surgical treatment [82].

Moreover, even after long-term remission is achieved, evidence suggests that Cushing's syndrome patients have increased morbidity and mortality [88–90]. Colao et al. found that patients cured from pituitary-dependent Cushing's syndrome for a long-term period had a higher body mass index (BMI), systolic and diastolic blood pressure, fasting glucose, cholesterol, low-density lipoprotein, and fibrinogen when compared to controls. This suggests that the increased cardiovascular risk from Cushing's syndrome persists even after remission, likely due to residual metabolic abnormalities [88]. This risk may persist irrespective of the initial degree of hypercortisolism [90]. Accordingly, it is critical that Cushing's syndrome patients are followed up long term and that their comorbidities are adequately treated.

Acromegaly

Acromegaly is a rare condition caused by the hypersecretion of growth hormone (GH), which is usually due to a GH-secreting pituitary adenoma [91]. The increase in GH consequently increases insulin-like growth factor 1 (IGF-1) which leads to the characteristic phenotype and systemic manifestations of the disorder. Recent studies have shown a prevalence ranging from 2.8 to 13.7 cases per 100,000 people with an annual incidence of about 0.2–1.1 cases per 100,000 people [92]. There is an estimated delay in diagnosis of about 4.5–5 years with median age of diagnosis in the fifth decade of life [92].

Clinical Manifestations

Excess GH in young patients prior to epiphyseal closure leads to gigantism, while acromegaly occurs if GH excess is present after epiphyseal closure [93]. The characteristic clinical features of acromegaly are summarized in Table 10.4 [91, 93–95]. Facial and acral overgrowth and soft tissue hypertrophy are some of the most notable signs of the condition [93]. These include prominent brow, enlarged nose and ears, thickened lips,

Table 10.4 Common clinical characteristics of acromegaly

System	Notable features
Orofacial	Prominent brow; enlarged nose and ears; thickened lips; marked skin wrinkles; prognathism; teeth separation; macroglossia
Cardiovascular	Hypertension; cardiomyopathy (especially left ventricular hypertrophy); congestive heart failure; valvulopathy; arrhythmias
Respiratory	Central or obstructive sleep apnea; snoring; respiratory insufficiency; upper airway narrowing
Gastrointestinal	Colonic polyps; dolichomegacolon
Skeletal	Degenerative arthritis; arthralgias; acromegalic osteopathy; vertebral fractures; peripheral neuropathy; carpal tunnel syndrome
Skin	Acral overgrowth; increased skin thickness and soft tissue hypertrophy; oily skin; hyperhidrosis; hypertrichosis; acanthosis nigricans; hirsutism; psoriasis; Raynaud's phenomenon
Reproductive	Abnormal menstrual cycles; erectile dysfunction
Psychological	Reduced self-esteem; anxiety; depression; social withdrawal
Endocrine/ metabolic	Thyroid goiter; insulin resistance; impaired glucose tolerance; diabetes mellitus; dyslipidemia (especially hypertriglyceridemia, low HDL)
Neoplastic	Colon cancer; thyroid cancer
Local tumor effects	Headache; visual disturbance; elevated prolactin; hypopituitarism

Modified with information from Colao et al. [91], Vilar et al. [93], Pivonello et al. [94], and Katznelson et al. [95]

macroglossia, and prognathism leading to dental malocclusion and teeth separation. Patients may note changes in shoe or ring size due to progressive growth of their hands and feet. A deepening of the voice may occur due to laryngeal hypertrophy [91, 93]. Headache is a common feature regardless of tumor size. As many of these tumors are diagnosed as macroadenomas, local tumor effects can lead to visual field deficits and hypopituitarism [91]. Common skin manifestations include skin thickening, oily skin, hyperhidrosis, and acanthosis nigricans [96]. Psoriasis has also been reported, and while the etiology is unclear, it has been associated with elevated GH levels with improvement noted with acromegaly treatment [96, 97]. Raynaud's phenomenon due to alterations in skin microcirculation may also be seen [96]. Acromegalic arthropathy is a degenerative arthritis that can affect all joints (most commonly the knee, hip, and shoulder) and that can continue to progress despite biochemical control of the disease [93, 98]. Acromegalic osteopathy is defined by increased bone turnover, degeneration of bone microstructure, and increased risk of vertebral fractures despite normal bone mineral density [93, 99]. Dorsal kyphosis, rib cage stiffening, arthralgias, ulnar nerve neuropathy, and carpal tunnel syndrome are also skeletal manifestations of this disease [93].

Cardiovascular, respiratory, metabolic, and neoplastic comorbidities and complications contribute to the increased mortality seen in acromegaly [94, 100]. Hypertension is diagnosed in about a third of patients. While the mechanism is unclear, its pathogenesis may be multifactorial due to direct or indirect effects of GH and/or IGF-1 on the kidneys causing sodium retention and plasma volume expansion [101]. Cardiac hypertrophy (mainly left ventricular hypertrophy), valvulopathy, congestive heart failure, arrhythmias, and endothelial dysfunction are also common features of acromegalic cardiac disease [94]. While central sleep apnea may be seen in acromegaly, obstructive sleep apnea is more common due to upper airway obstruction from macroglossia, hypertrophy of the respiratory mucosa and cartilage, and other changes to the craniofacial architecture [93, 94]. Dorsal kyphosis, distortion of the rib cage, and changes in lung volume contribute to respiratory insufficiency as well [94]. Excess growth hormone has been associated with increased lipolysis, impaired pancreatic beta-cell function, and increased gluconeogenesis in the liver leading to insulin resistance, impaired glucose tolerance, and diabetes mellitus [94]. Lipid metabolism is also altered in acromegaly leading to dyslipidemia, namely, hypertriglyceridemia and reduction in HDL cholesterol [94]. Increased risk of colonic polyps and nodular goiter have also been reported [100].

Diagnosis

Current Endocrine Society guidelines recommend that patients who present with clinical features or comorbid conditions suggestive of acromegaly or who have a pituitary mass should have an IGF-1 level measured [95]. IGF-1 is considered the best biochemical marker of disease activity. Unlike GH, it is not pulsatile, has a longer half-life, and has less variability over the course of the day [102]. If the IGF-1 level is elevated or equivocal, it is recommended that a confirmatory test with an oral glucose tolerance test (OGTT) be performed with diagnosis confirmed by an unsuppressed GH level >1 μg/L after a glucose load confirmed hyperglycemia [95]. Of note, the OGTT in patients with baseline impaired glucose metabolism may be difficult to interpret as GH levels do not suppress normally after OGTT in these patients leading to potential false-positive results. However, if diabetes is well-controlled and a highly sensitive GH assay is used with a cutoff GH nadir 0.4 μg/L, the OGTT may still be used to evaluate patients with impaired glucose metabolism and suspected acromegaly [103]. It is not recommended to check a random GH level as high GH levels may be found in healthy patients due to normal episodic secretion of GH [95]. Once a biochemical diagnosis of acromegaly has been established, pituitary imaging, preferably a pituitary MRI, is recommended.

Given the significance of the GH and IGF-1 assays in diagnosing acromegaly and monitoring disease activity, there are several caveats that are important to note in the interpretation of these tests. IGF-1 and GH levels can be altered by many factors, such as age, BMI, nutritional status, pregnancy, abnormal liver or kidney function, hormone replacement therapy, and poorly controlled diabetes [91, 95, 104]. This can lead to discordance of IGF-1 and GH levels. At high GH levels (>20 μg/L or >40 mU/I), there is also no longer a linear relationship between IGF-1 and GH as IGF-1 levels plateau [102, 105]. There can also be considerable variability between different IGF-1 immunoassays due to differences in antibody specificity, interfering IGF-1 binding proteins, normative data, and reference ranges [106]. Some of the limitations of immunoassays can be overcome by measuring IGF-1 levels via a standardized tandem liquid chromatography and mass spectrometry (LC-MS) assay, but switching assays can lead to discordant results which must be interpreted appropriately when making management decisions [107]. It is therefore recommended to use the same IGF-1 assay throughout the management of patients with acromegaly [95].

Differential Diagnosis

Some patients may have the clinical features of acromegaly but have normal IGF-1 and GH levels ("pseudoacromegaly"). For example, acute hemorrhage or infarction of a somatotroph adenoma (pituitary apoplexy) can lead to spontaneous remission of acromegaly [108]. Pachydermoperiostosis (hypertrophic pulmonary osteoarthropathy) is a rare autosomal recessive genetic disorder associated with elevated prostaglandin E2 levels that can be misdiagnosed as acromegaly as patients can present with coarsened facial features, acral enlargement, and hyperhidrosis. However, these patients have markedly greater skin thickening than acromegaly with scalp skin folds resembling brain gyri ("cutis verticis gyrata") along with digital clubbing and periosteal ossification [109]. Patients with severe insulin resistance can also present with acromegalic features but have normal GH and IGF-1 levels and have a normal pituitary MRI [110]. Primary hypothyroidism and the use of certain medications such as minoxidil have also been associated with acromegaloid features [111, 112]. Other genetic conditions associated with acromegalic features, such as Sotos syndrome, could also be considered in the differential diagnosis of acromegaly [113].

Management

The goals of treatment of acromegaly are normalization of IGF-1 accounting for age and sex and undetectable GH levels (<1 μg/L) after OGTT

[95]. This has been shown to reduce excess mortality in acromegaly and to reduce the risk of comorbid conditions which also contribute to increased mortality [114, 115]. Surgical resection with transsphenoidal surgery is the first-line treatment. Repeat surgery should be considered in those who have residual disease [95]. While preoperative medical management of acromegaly can improve the chance of surgical cure, it is not routinely recommended as data on postoperative outcomes is undefined [95, 116]. Current guidelines support the use of preoperative medical therapy in those with increased anesthetic risk due to pharyngeal thickening, sleep apnea, or high-output heart failure [95]. Medical management should be considered in those who are not operative candidates or who have persistent disease postoperatively.

There are several clinical and pathological factors to consider when choosing the appropriate medical therapy for patients with acromegaly. The first-generation somatostatin receptor ligands (SRLs), octreotide long-acting release (LAR) and lanreotide autogel, are considered first-line medical therapy for acromegaly [95, 115]. These medications have an affinity for somatostatin receptor type 2 (SST2). Predictors of treatment response include the pathology of the tumor and the intensity of the tumor on MR imaging. Tumors that are densely granulated tend to have higher SST2 expression and have better response to SRL therapy than sparsely granulated tumors. On T2-weighted MR images, hypointense tumors are more likely to respond to SRL therapy than hyperintense tumors [95, 115, 117]. The dopamine agonist, cabergoline, can be considered as first-line treatment in milder disease when the IGF-1 level is less than 2.5 times the upper limit of normal [115].

If disease control is not achieved with uptitration of first-generation SRL therapy or the addition of cabergoline, second-line medical therapy should be considered. The choice of second-line therapy depends on certain clinical characteristics. If there is concern for tumor growth, the second-generation SRL, pasireotide, which has affinity for multiple SST receptors (especially SST5) can be considered [115]. The PAOLA trial demonstrated that switching to pasireotide can be effective and safe in patients who had an inadequate response to first-generation SRLs, though a notable side effect was hyperglycemia [118]. If there is concern for impaired glucose metabolism, the GH receptor antagonist, pegvisomant, is preferred. Of note, since pegvisomant does not have direct antiproliferative effects on tumor cells, GH hypersecretion persists, so IGF-1 is the only marker of drug efficacy [95]. ACROSTUDY is an international surveillance study that has evaluated the long-term safety and outcomes of pegvisomant treatment [119]. It has shown increased IGF-1 level normalization rates over time and that abnormal liver function tests and tumor growth are rare side effects of pegvisomant therapy [115, 119]. If there is poor response to treatment, tumor concerns, and impaired glucose metabolism, pegvisomant can be added to first-generation SRL therapy [115]. Stereotactic radiosurgery or the alkylating agent temozolomide can be considered as third-line therapy if the above interventions are unsuccessful [95, 115].

One of the newer therapies being investigated for acromegaly is oral octreotide, which has been shown to be effective in maintaining biochemical control of acromegaly in patients who were switched to this treatment from first-generation SRL therapy [120, 121]. It has been shown to have a similar safety profile to the first-generation SRLs. It was recently FDA approved for the treatment of patients with acromegaly who previously responded to octreotide LAR or lanreotide autogel based on the results of two recent phase 3 clinical trials: the Maintenance of Acromegaly Patients with Octreotide Capsules Compared with Injections-Evaluation of Response Durability (MPOWERED™) and Octreotide Capsules vs. Placebo Treatment in Multinational Centers (CHIASMA OPTIMAL) [121–123]. A summary of the medications used in the medical management of acromegaly is provided in Table 10.5 [95, 115, 117, 120].

In addition, all patients with acromegaly should be evaluated for comorbid conditions such as hypertension, diabetes mellitus, cardiovascular disease, and obstructive sleep apnea as these must be aggressively managed [95]. Other pituitary axes should be evaluated for hypopituitarism to replace any deficits [95, 124]. Screening colonoscopy is recommended at the time of diag-

Table 10.5 Medical management of acromegaly

Medication	Formulation	Notable side effects
First-generation SRL		
Octreotide LAR	10–40 mg (starting dose 20 mg) once monthly IM injection	Nausea, abdominal pain, diarrhea, constipation, cholelithiasis, hyperglycemia
Lanreotide autogel	60–120 mg (starting dose 90 mg) once monthly SQ injection	
Second-generation SRL		
Pasireotide	40–60 mg once monthly IM injection	Similar to first-generation SRL but with greater hyperglycemia
Dopamine agonist		
Cabergoline	1–4 mg oral tablet once or twice weekly	Nausea, dizziness, orthostasis, mood disorder, risk of cardiac valve abnormality (high doses)
GH receptor antagonist		
Pegvisomant	10, 15, or 20 mg daily SQ injection	Improved insulin resistance, abnormal liver function tests, lipodystrophy, possible pituitary tumor growth
Recently FDA approved		
Oral octreotide	40–80 mg oral tablet divided twice daily	Similar to first-generation SRL

Modified with information from Melmed et al. [115], Katznelson et al. [95], Melmed et al. [120], and Zahr et al. [117]
Abbreviations: *SRL* somatostatin receptor ligand, *SST* somatostatin receptor, *IM* intramuscular, *SQ* subcutaneous, *GH* growth hormone

Table 10.6 Recommendations for screening for comorbid conditions in acromegaly

Colon cancer	Screening colonoscopy at the time of diagnosis with appropriate follow-up (e.g., every 10 years if no colonic polyps and IGF-1 level normalized)
Thyroid disease	Thyroid ultrasound if palpable thyroid nodules on exam Annual FT4 level
Impaired glucose tolerance	Fasting blood glucose or OGTT every 6 months If diabetes or prediabetes, check HbA1c every 6 months
Adrenal insufficiency	If suspected, check AM cortisol between 8 and 9 AM. If low, confirm with cosyntropin stimulation test
Hypogonadism	Male: annual total testosterone and sex hormone-binding globulin levels Female: annual luteinizing hormone, follicle-stimulating hormone, and estradiol levels if premenopausal with abnormal menstrual periods or desiring pregnancy Both: prolactin
Osteoporosis	DEXA every 2 years Annual vertebral morphometry, especially if there is history of or suspected vertebral fracture, hypogonadism, and uncontrolled acromegaly
Cardiovascular disease	Annual echocardiography if abnormal Annual electrocardiogram if abnormal Baseline blood pressure measurement with monitoring every 6 months or sooner if change in medication
Sleep apnea	Epworth sleepiness scale or sleep study if OSA suspected

Modified with information from Katznelson et al. [95] and Giustina et al. [124]
Abbreviations: *IGF-1* insulin-like growth factor 1, *FT4* free thyroxine, *OGTT* oral glucose tolerance test, *HbA1c* hemoglobin A1c, *OSA* obstructive sleep apnea

nosis given the increased risk of colonic polyps with appropriate surveillance thereafter [93, 95]. Since there is increased risk of nodular thyroid disease, a thyroid ultrasound is recommended if there are palpable thyroid nodules on exam [95]. Due to the high risk of vertebral fractures despite normal bone mineral density, additional imaging such as bone morphometry studies is recommended as dual-energy x-ray absorptiometry may not be reliable to predict fracture risk [124, 125]. Screening recommendations for acromegaly are summarized in Table 10.6 [95, 124].

Thyrotropin-Secreting Pituitary Adenomas

Thyrotropin (TSH)-secreting pituitary adenomas (TSHomas) are the rarest form of pituitary adenoma, accounting for 0.5–3% of all pituitary tumors [126], and an even rarer cause of hyperthyroidism [127, 128]. They are generally benign tumors, characterized by autonomous TSH secretion that is unresponsive to negative feedback by thyroid hormone. The result is overstimulation of the thyroid gland to hypersecrete thyroid hormones (T3 and T4) [129]. The prevalence of TSHomas is estimated to be about 1–2.8 cases per million [130, 131], with no difference in prevalence between males and females [126]. However, the number of reported TSHomas has risen rapidly in the last decade, likely due to increased clinician awareness and the introduction of ultrasensitive TSH assays [131–133].

Clinical Manifestations

While it is thought that about a quarter of TSHomas are clinically silent [133], patients with TSHomas often present with mild-to-moderate hyperthyroidism features such as weight loss, fatigue, tachycardia, irritability, insomnia, anxiety, sweating, and heat intolerance [134]. The prevalence of clinical manifestations is summarized in Table 10.7 [126, 132, 135]. The most common feature is uninodular or multinodular goiters, present in approximately 70–90% of cases [126, 132]. However, the progression to toxic goiter is infrequent [136]. In addition, the clinical features of hyperthyroidism may be milder in TSHomas than expected for the given level of thyroid hormone, with the more severe consequences of hyperthyroidism such as atrial fibrillation or cardiac failure being rare [137]. Notably, the pathognomonic signs for Graves' disease, ophthalmopathy and pretibial myxedema, will be absent.

About one quarter of TSHomas are plurihormonal [132] with co-secretion of GH or prolactin being the most common [138]. In cases of mixed TSH- and growth hormone (GH)-secreting adenomas, the signs and symptoms of hyperthyroidism may be masked by those of acromegaly [129]. Moreover, because TSHomas are often large and invasive, patients may have signs and symptoms due to mass effect, such as visual field defects, headache, and hypopituitarism [139].

Table 10.7 Clinical manifestations in patients with TSHoma by prevalence

Signs and symptoms	Frequency (%)
Goiter	70–93%
Thyroid nodules	70–77%
Visual field defects	35%
Menstrual disorders	33%
Previous thyroidectomy	29%
Galactorrhea	28%
Severe thyrotoxicosis	21%
Headache	21%
Acromegaly	16%

Modified from Beck-Peccoz et al. [132], Amlashi and Tritos [126], Brucker-Davis et al. [135]

The gonadal axis is the most frequently affected, manifesting as menstrual irregularities, delayed puberty, and decreased libido [137]. However, more TSHomas are being diagnosed at the stage of microadenoma due to advances in the sensitivity of TSH and thyroid hormone immunometric assays [138].

Diagnosis

Early diagnosis is imperative, as untreated hyperthyroidism can have significant hemodynamic effects on the cardiovascular system, resulting in palpitations, arrhythmias, and cardiac failure [138, 140]. Even in cases of subclinical hyperthyroidism, there is increased risk of total mortality and mortality due to coronary heart disease and atrial fibrillation [141]. The diagnosis of a TSHoma is based on an elevated or inappropriately normal TSH level, an elevated T3 and T4, and a pituitary tumor on MRI [128]. This is in contrast to more common causes of primary hyperthyroidism such as Graves' disease, in which hypersecretion of thyroid hormone results in low or undetectable TSH levels via negative feedback. Nevertheless, TSHomas are misdiagnosed as primary hyperthyroidism disease frequently, with approximately

30% undergoing inappropriate thyroidectomy or radioiodine thyroid ablation. Nowadays, serum TSH is measured with ultrasensitive immunometric assays and circulating free thyroid hormones with direct immunoassays, aiding in the distinction between these two clinical entities and leading to earlier diagnoses [132]. However, circulating factors such as anti-iodothyronine autoantibodies, abnormal forms of albumin or transthyretin, and heterophilic antibodies may interfere with the measurement of total and free thyroid hormone or TSH [130]. Accordingly, it is critical that methodological interference is excluded when making the diagnosis.

Along with measurements of serum TSH and thyroid hormone, serum α-subunit, T3 suppression, and thyrotropin-releasing hormone (TRH) tests are also recommended to improve the specificity and sensitivity of the diagnosis [135]. In most patients with TSHomas, especially macroadenomas, serum concentrations of the α-subunit of glycoprotein hormones are elevated. The relative increase in the α-subunit is greater than that of the serum TSH, resulting in a higher molar ratio of serum α-subunit to TSH [130]. Dynamic testing with T3 and TRH is also useful. To perform a T3 suppression test, 80–100 μg is given orally for 8–10 days. Normally, this would result in complete inhibition of TSH secretion; however, there is a lack of complete TSH inhibition in TSHoma patients [132]. To perform a TRH stimulatory test, a 200–500 μg intravenous injection of TRH is given with subsequent TSH measurements. In patients with TSHoma, TRH often fails to stimulate TSH secretion [130].

The diagnosis of TSHoma is ultimately confirmed with pathology. TSHomas will stain for the TSH beta-subunit, either free or combined with α-subunit of any glycoprotein hormone (α-GSU) [129]. In addition, the 2017 World Health Organization (WHO) classification of pituitary tumors classifies adenomas by their pituitary cell lineage, rather than by which hormone is produced by the adenoma. Along with somatotroph and lactotroph adenomas, TSHomas express strong nuclear staining for the acidophilic lineage transcription factor known as pituitary-specific POU-class homeodomain transcription factor (PIT-1). In contrast, corticotroph and gonadotroph adenomas are negative for PIT-1 expression [142].

Differential Diagnosis

After biochemical testing confirms hyperthyroidism without TSH suppression, resistance to thyroid hormone action (RTH) must be excluded. Like TSHomas, RTH is a rare disease, similarly characterized by elevated free thyroid hormones and unsuppressed TSH. RTH is caused by dominant negative mutations in the thyroid hormone receptor, most frequently the beta-subunit, causing variable tissue hyposensitivity to thyroid hormone. Unlike the autonomous secretion of TSH by TSHomas, thyrotropes in patients with RTH are refractory to the negative feedback from high thyroid hormone levels, such that TSH secretion persists [143, 144]. Collectively, the two syndromes are referred to as "inappropriate TSH secretion" or "central hyperthyroidism." Once the diagnosis of central hyperthyroidism has been made, it is critical that TSHomas and RTH are distinguished. Factors aiding in this distinction are summarized in Table 10.8 [132]. Though the presence of an adenoma on pituitary MRI or CT strongly supports the diagnosis of TSHoma, RTH may occur in the presence of a pituitary incidentaloma. Thus, imaging should be supplemented with biochemical data. For example, sensitivity to somatostatin and its analogs has been proposed to distinguish TSHomas: multiple injections of long-acting somatostatin analogs result in a marked decrease in free T3 and T4 lev-

Table 10.8 Differential diagnosis between TSH-secreting pituitary adenoma (TSHoma) and resistance to thyroid hormone action (RTH)

Feature	TSHoma	RTH
α-Subunit	Elevated	Normal
Pituitary imaging	Positive	Negative
Response to TRH test	Absent	Present
T3 suppression test	Absent	Present
Family history	No	Yes
Molecular studies	No	Mutations in thyroid hormone receptor-β

Modified from Beck-Peccoz et al. [132]

els in patients with TSHomas, whereas patients with RTH do not respond [132].

Management

In patients with TSHomas, the primary aim of treatment is to achieve a euthyroid state and correct symptoms related to mass effect. Surgical resection is the first-line treatment [145], though preoperative medical treatment with somatostatin analogs such as octreotide and lanreotide can help normalize thyroid hormone levels, reduce tumor size, and improve surgical outcomes [138]. Additional preoperative treatment with antithyroid drugs and beta-blockers may be employed in cases of severe hyperthyroidism, reducing the perioperative risk of thyroid storm [146]. Occasionally, temporary postoperative thyroid hormone replacement may be needed in patients with successful surgery [138].

Nonetheless, many studies report postoperative remission rates to be relatively poor (0–63%) [138, 147–150]. Generally, this is attributed to the fibrotic nature and invasiveness of these tumors, making complete surgical removal extremely difficult [137]. However, a large case series by Yamada et al. reported a remission rate of 84% with aggressive treatment of tumors with cavernous sinus invasion and giant adenomas [138]. While the prognostic factors for surgical treatment of TSHomas have not been well established, large tumor size, cavernous sinus invasion, and fibrosis have been associated with poorer surgical outcomes [133, 138].

The risk of recurrence is relatively low after successful surgery (estimated 3–10%) [133, 151]. With most recurrences occurring within the first 2–3 years postoperatively [150, 151], close follow-up should be performed in all patients during this period. Still, most patients are in need of medical therapy or radiation treatment after surgery. Somatostatin analogs are the most widely used and highly efficacious, normalizing thyroid hormone levels in 80–95% of patients [132, 152] and resulting in tumor shrinkage in 40–61% [132, 133]. Other less frequently used medical treatments include antithyroid drugs and dopamine agonists. In patients with persistent disease, radiotherapy can be an effective method for controlling TSH hypersecretion and tumor growth, normalizing thyroid hormone levels in 20–50% of patients, and reducing tumor volume in 26%. The effects are greatest within the first years after surgery, though hypopituitarism occurs in approximately one-third of patients [151].

Gonadotroph Adenomas (Gonadotrophinomas)

Gonadotroph adenomas can be divided into functioning and nonfunctioning adenomas. The 2017 World Health Organization (WHO) classification for endocrine tumors defines pituitary adenomas according to their pituitary hormone and transcription factor profile. Included in this classification are nonfunctioning pituitary adenomas (NFPAs), which are benign neoplasms that are not associated with any clinical manifestations of hormonal hypersecretion [153]. Nonfunctioning pituitary adenomas (NFPAs) usually manifest by presence of mass effect symptoms such as visual changes, headaches, and hypopituitarism and are characterized by the absence of clinical symptoms due to hormone hypersecretion [154]. They can either be "totally silent," where the adenomas do not secrete sufficient amounts of hormonal products to cause an elevation of the serum concentration, or "clinically silent," where the hormonal products do not result in clinical signs or symptoms typical of that hormone [155]. The most common type of clinically nonfunctioning adenomas are silent gonadotroph adenomas [4]. Functioning gonadotroph adenomas (FGAs) are adenomas that express and secrete biologically active gonadotropins resulting in clinical manifestations of hormone excess [156]. These adenomas can produce and secrete FSH, LH, alpha-subunit, FSH beta-subunit, and/or LH subunit [157].

Clinical Manifestations and Diagnosis

Clinical manifestations of FGAs include infertility and ovarian hyperstimulation syndrome

(OHSS) in women, testicular hypertrophy and sexual dysfunction in men, and isosexual precocious puberty in children [158, 159]. In premenopausal women, clinical manifestations include menstrual irregularities, for example, secondary amenorrhea, oligomenorrhea, spontaneous vaginal spotting, and severe menorrhagia. Other findings include infertility, galactorrhea, and mass effect symptoms, such as headaches and vision changes. Additionally, a rare presentation in premenopausal women includes ovarian hyperstimulation syndrome (OHSS) [156]. OHSS usually presents as an iatrogenic complication of ovulation induction treatment using human menopausal gonadotropin combined with human chorionic gonadotropin, resulting in enlarged multicystic ovaries [160]. It is thought that the stimulated ovaries overproduce vascular endothelial growth factor (VEGF), which causes systemic increase in vessel permeability and subsequent extravasation of fluid into the peritoneal cavity and third space, manifesting as ascites and peripheral edema [160, 161].

Functioning gonadotroph adenomas associated with OHSS commonly present with menstrual disorders including amenorrhea, oligomenorrhea, and irregular menses. Patients also complain of increased abdominal girth and distention, abdominal or pelvic pain and discomfort due to enlarged ovaries and irritation of the peritoneum, and difficulty conceiving. Some other less common symptoms include galactorrhea, nausea, and vomiting [156, 162]. Compared to iatrogenic OHSS, ovarian hyperstimulation syndrome caused by gonadotropin-secreting adenomas does not typically present with ascites or hypercoagulability, despite high concentrations of estradiol or FSH. Ultrasound examination findings include enlarged bilateral ovaries with multiseptated cysts of variable size, typically greater than 5 cm in diameter, which is much larger than the 3 cm-or-smaller cysts found in polycystic ovaries [156, 159, 161]. There are enlarged follicles arranged peripherally around ovarian parenchyma causing the cysts to have a characteristic "soap-bubble" or "wheel-spoke" appearance, with pseudosepta formed by compression of normal stroma between follicles [156, 159].

The characteristic hormonal profile has normal-to-elevated FSH levels, suppressed LH levels, elevated estradiol levels, and supranormal concentrations of prolactin, most commonly due to pituitary stalk compression. The elevated or inappropriately normal FSH level supports the theory of impaired negative feedback in these cases due to secretion by these adenomas. Low levels of LH are typically thought to be due to the estrogen-induced negative feedback or compression of normal pituitary tissue [162]. Elevated inhibin levels can also be seen because FSH stimulates luteinized granulosa cells to produce inhibin A so levels will be elevated with increased secretion of FSH [163]. Gonadotroph adenomas may secrete gonadotropins in their complete forms or as subunits so patients may have elevated alpha-subunits [164].

In postmenopausal women, there is no typical clinical syndrome that manifests as the ovaries are depleted of preantral follicles and no longer sensitive to FSH stimulation. However, patients may have symptoms related to mass effect. Given that FSH and LH levels rise in postmenopausal women, it can also be difficult to interpret increased FSH as related to the adenoma or from menopause. A differentiating factor can be an elevated FSH with a suppressed LH [156].

In males, clinical manifestations of FSH-producing FGAs include testicular enlargement and increased length of seminiferous tubules, hypogonadism, and visual disturbance from mass effect. Regarding the hormonal profile seen in these cases, FSH levels are typically elevated. LH and testosterone levels are slightly below normal, normal, or elevated. There have also been cases with elevated inhibin or alpha-subunit levels [156]. In cases with testicular enlargement, ultrasound of the scrotum shows increased testicular volume without cystic or solid masses seen. Both increased spermatogenesis and hypospermatogenesis have been reported in cases [156].

In children, FGAs are rare, but they have been shown to present with isosexual precocious puberty. Clinical manifestations include accelerated breast or pubic/axillary hair development, OHSS in girls, and accelerated pubic hair and genital development in males. Mass effect symp-

Table 10.9 Clinical manifestations and laboratory findings in pre- and postmenopausal women, males, and children with functioning gonadotroph adenomas

Type of patient	Clinical manifestations	Common laboratory findings
Premenopausal women	>Menstrual irregularities (amenorrhea, oligomenorrhea, vaginal spotting, menorrhagia) >Infertility >Galactorrhea >Ovarian hyperstimulation syndrome (OHSS) >Mass effect symptoms	↑ or normal FSH ↓ or normal LH ↑ estradiol ↑ or normal alpha-subunit ↑ or normal inhibin
Postmenopausal women	>Mass effect symptoms	Often noncontributory as postmenopausal women have elevated FSH and LH levels
Males	>Testicular enlargement, increased seminiferous tubule length >Hypogonadism >Mass effect symptoms	↑ FSH ↓, ↑, or normal LH ↓, ↑, or normal testosterone ↑ or normal alpha-subunit ↑ or normal inhibin
Children	>Isosexual precocious puberty: Girls: accelerated breast and pubic/axillary hair development, OHSS Boys: accelerated pubic hair and genital development >Mass effect symptoms	↑ FSH ↓ or ↑ LH ↑ estradiol ↑ testosterone (boys)

Modified from Ntali et al. [156]
Abbreviations: *FSH* follicle-stimulating hormone, *LH* luteinizing hormone

toms such as vision changes have also been seen. In cases in children, hormonal profiles have shown elevated FSH levels, either low or elevated LH levels, and elevated prolactin levels. In girls, elevated estradiol levels have also been seen, similar to other premenopausal females, and in males, elevated testosterone levels have been seen [156].

When an FGA is suspected based on clinical presentation, initial diagnosis is based upon hormonal profiles as described in Table 10.9 and finding a sellar mass on MRI [156]. Findings such as suprasellar extension, optic chiasm compression, and cavernous sinus invasion can be seen on imaging [159, 165].

Differential Diagnosis

When OHSS is suspected due to an FSH-secreting adenoma, other conditions on the differential need to be evaluated. These include polycystic ovarian syndrome (PCOS), OHSS attributed to other causes, and ovarian neoplasms [156]. PCOS causes enlarged multicystic ovaries; however, the cysts are typically smaller than those in OHSS, and patients also have symptoms of hyperandrogenism including hirsutism, acne, and alopecia [166]. OHSS attributed to other causes includes iatrogenic complications of ovulation induction, spontaneous OHSS associated with severe primary hypothyroidism, ectopic secretion of FSH from carcinoid tumor, and association with normal and abnormal pregnancies [156, 157, 160, 162]. Ovarian malignancies that can lead to multicystic ovaries include serous cystadenomas and mucinous cystadenomas, which can lead to ovaries with thin-walled, large cysts [167].

In males, FGAs can present with testicular enlargement. Other diagnoses that cause testicular enlargement and need to be assessed include microlithiasis, McCune-Albright syndrome, congenital testicular cysts, malignant testicular lesions, lymphomas, acute lymphoblastic leukemia, infection, aromatase deficiency, and macroorchidism caused by fragile X syndrome [156].

Functioning gonadotroph adenomas in children typically present with isosexual precocious puberty. The differential diagnosis for isosexual precocious puberty is also broad and has to be evaluated for in these cases, including central nervous system lesions (such as arachnoid cysts,

craniopharyngiomas, ependymomas, germinomas, low-grade gliomas), developmental anomalies (such as hydrocephalus and hypothalamic hamartomas), postirradiation, genetic causes, and primary hypothyroidism [156].

Management

The optimal approach to management of FGAs is surgical removal via transsphenoidal resection. Successful removal of the tumor results in the return of normal gonadotropin secretion as well as resolution of OHSS and return of regular menses in women, reduction of testicular volume in males, and appropriate pubertal status patterns in children [156]. Persistence and/or recurrence of these tumors may occur, requiring repeat surgical resection. Radiation therapy can be used as adjunct therapy after surgery, more commonly in cases of recurrent adenomas [145]. Medical therapy options include dopamine agonists such as bromocriptine and cabergoline, somatostatin receptor ligands such as octreotide, gonadotroph-releasing hormone agonists, and gonadotroph-releasing hormone antagonists. These have been tried as both first-line therapies and after transsphenoidal surgery and in the majority of cases have shown little benefit for improving clinical symptoms and have not been shown to be effective in tumor shrinkage [145, 156].

Syndrome of Inappropriate Antidiuretic Hormone

Arginine vasopressin (AVP) is a hormone that is synthesized mainly by magnocellular neurons in the hypothalamus and stored in neurosecretory granules in the posterior pituitary gland [168]. Its release is triggered by activation of osmoreceptors in the hypothalamus in response to high plasma osmolality. Its secretion can also be non-osmotically stimulated by baroreceptors at various locations (carotid sinus, aortic arch, and left atrium) in response to low blood pressure or blood volume. It binds to its receptor, V2 receptor, in the renal collecting ducts leading to an antidiuretic effect [168].

Dysregulation of AVP secretion can lead to hyponatremia ([Na+] < 135 mEq/L), which is a common electrolyte disorder that is observed in about 15–30% of acutely hospitalized patients and 7–21% of ambulatory patients [169]. It is associated with increased morbidity and mortality even in mild cases with [Na+] 130–134 mEq/L [170]. Depending on the plasma osmolality, hyponatremia can be classified as hypotonic, isotonic, or hypertonic. Hypotonic hyponatremia can be further differentiated as hypovolemic, euvolemic, or hypervolemic based upon a patient's fluid status. The syndrome of inappropriate antidiuretic hormone (SIADH) is diagnosed in euvolemic patients and is the most common cause of hyponatremia [171]. In SIADH, AVP levels are elevated despite low plasma osmolality, which would normally osmotically suppress AVP secretion from the posterior pituitary [172]. Numerous conditions have been associated with SIADH and are summarized in Table 10.10 [172, 173].

Clinical Manifestations

Symptoms of hyponatremia are mainly neurological as a result of the osmotic fluid shifts into the brain that can lead to cerebral edema [174]. This can have deleterious effects due to the limited boundaries of the skull, and brain herniation from increased intracranial pressure is a fatal complication [174, 175]. The acuity of the hyponatremia determines whether the brain has had enough time to adapt to the osmotic fluid shifts by extrusion of intracellular solutes [174, 176]. Patients with acute hyponatremia (<48 hours) are thus typically more symptomatic than those with chronic hyponatremia (>48 hours) as the brain has not had enough time to make this adjustment [176]. The early symptoms of hyponatremic encephalopathy include headache, weakness, muscle aches, nausea, and vomiting [174]. As cerebral edema progresses, altered mentation, respiratory failure, seizure, coma, and death may be seen. The

Table 10.10 Possible etiologies of SIADH

Malignancy
Certain lung cancers (bronchogenic carcinoma, mesothelioma)
Thymoma
Gastrointestinal cancer
Pancreatic cancer
Uterine cancer
Prostate cancer
Leukemia/lymphoma
Brain tumors
Central nervous system abnormality
Head trauma
Subarachnoid hemorrhage or subdural hematoma
Multiple sclerosis
Guillain-Barré syndrome
Post-resection of pituitary mass or section of pituitary stalk
Iatrogenic (medications)
Desmopressin
Oxytocin
Indomethacin
Carbamazepine
Oxcarbazepine
Chlorpropamide
Clozapine
Serotonin reuptake inhibitors
Lisinopril
Omeprazole
3,4-Methylenedioxymethamphetamine (MDMA, "Ecstasy")
Pulmonary
Acute respiratory failure
Mechanical ventilation
Severe chronic obstructive pulmonary disease
Infection
Brain abscess
Encephalitis/meningitis
Tuberculosis
Aspergillosis
Viral or bacterial pneumonia
Acquired immunodeficiency syndrome
Others
Idiopathic
Prolonged rigorous exercise

Modified with information from Verbalis et al. [172] and Ellison et al. [173]

magnitude of the hyponatremia is also an important factor as severe symptoms are not typically seen unless [Na+] < 125 mEq/L [176]. Importantly, patients who are seemingly asymptomatic with chronic hyponatremia may actually have some underlying neurological deficits, such as gait instability or inattention, which can increase the risk of falls and subsequent complications [172, 177].

Table 10.11 Main diagnostic criteria for SIADH

Decreased plasma osmolality (Posm <275 mOsm/kg H_2O)
Inappropriately concentrated urine (Uosm >100 mOsm/kg H_2O) despite hypoosmolality with normal renal function
Clinically euvolemic
Elevated urinary sodium (UNa > 40 mEq/L) with normal salt and fluid intake
Excluded hypothyroidism, adrenal insufficiency, and use of diuretics

Modified with information from Verbalis et al. [172] and Ellison et al. [173]
Abbreviations: *Posm* plasma osmolality, *Uosm* urine osmolality, *Una* urine sodium

Diagnosis

The criteria for the diagnosis of SIADH are summarized in Table 10.11 [172, 173]. It is first important to confirm low plasma osmolality (<275 mOsm/kg of H_2O) in order to rule out pseudohyponatremia from markedly elevated protein and lipid levels (isotonic hyponatremia) and dilutional hyponatremia caused by hyperglycemia (hypertonic hyponatremia). Urine osmolality should be checked to confirm an inappropriately concentrated urine (>100 mOsm/kg H_2O) in the setting of hypoosmolality [172]. Another essential diagnostic criterion is clinical euvolemia, which may be suggested by the absence of orthostasis, normal skin turgor, normal heart rate, and moist mucosa. Renal salt loss (urine sodium >40 mEq/L) helps differentiae hypoosmolality from reduced intravascular volume (preserved renal sodium reabsorption) and natriuresis from extracellular volume expansion. However, it is important to consider that renal sodium concentration may be increased due to diuretic use, glucocorticoid deficiency, or a restricted salt diet [172].

Differential Diagnosis

Overall, SIADH is a diagnosis of exclusion. Adrenal insufficiency (AI) can also cause hypotonic hyponatremia due to antidiuresis from direct effects on the kidneys as well as non-osmotically stimulated AVP secretion [172, 176]. While dynamic testing with cosyntropin stimulation is preferred when AI is clinically suspected, this may

be misleading if the deficiency is relatively acute and adrenal atrophy has not yet occurred [172]. In such cases with acutely ill patients, an early morning cortisol level can empirically be used to assess the hypothalamic-pituitary-adrenal axis with deficiency suggested by an inappropriate cortisol level below 5 μg/dl [178, 179]. Hypothyroidism, particularly if severe, has been associated with impaired diuresis that is thought to be due to the renal insufficiency that results from the low cardiac output and increased peripheral vascular resistance associated with hypothyroidism [180]. Primary polydipsia, low-solute diets (low-protein or "tea and toast" diets), and exercise-associated hyponatremia are also considered in the differential for euvolemic hyponatremia [172]. Cerebral salt wasting is a relatively rare condition that can be difficult to differentiate from SIADH as it is also associated with subarachnoid hemorrhage and neurosurgical procedures [172, 179]. It is characterized by natriuresis with subsequently reduced intravascular volume leading to a secondary elevation in AVP that results in water retention and hyponatremia.

Management

Curative treatment of SIADH is treatment of the underlying cause, such as discontinuing culprit medications or treating underlying malignancy [173]. The interim management of SIADH depends on the acuity and severity of the hyponatremia. If the hyponatremia is acute (<48 hours), the goal of treatment is prompt correction of sodium by 4–6 mEq/L to reduce the sequelae of cerebral edema [172]. This is usually achieved with a 100 mL bolus of hypertonic (3%) saline administered intravenously over 10 minutes [172, 181]. If symptoms are mild and there is a low risk of brain herniation, an infusion of 3% saline at 0.5–2 mL/Kg per hour can be considered. In chronic hyponatremia (>48 hours), the goal is to avoid rapid overcorrection of sodium as this can lead to osmotic demyelination [172]. Treatment is adjusted to correct sodium 4–8 mEq/L in the first 24 hours with a lower goal of 4–6 mEq/L per day if there is a high risk of osmotic demyelination [172]. Risk factors for osmotic demyelination include malnutrition, alcoholism, advanced liver disease, hypokalemia, and serum sodium levels less than 105 mEq/L [172]. If overcorrection occurs (greater than 6–8 mEq/L per day), then replacement of water loss with 5% dextrose in water or desmopressin should be considered [172, 181].

The treatment of SIADH, which is usually a chronic hyponatremia, is summarized in Table 10.12 [172, 181, 182]. The first-line treatment for SIADH is fluid restriction [172, 181].

Table 10.12 Summary of the treatment of SIADH (chronic hyponatremia)

Intervention	Administration	Complications/limitations
Fluid restriction (first-line)	Restrict all fluids (including intravenous) Degree of restriction can be estimated by urine-to-serum electrolyte ratio Ratio >1, restrict 500 mL per day Ratio <1, restrict 1 L per day	Poor adherence Predictors of poor response[a]
Demeclocycline (off-label)	Oral 600–1200 mg per day in divided doses	Nephrotoxicity Photosensitive rash
Urea	Oral 15–60 g per day	Poor palatability Increased serum BUN
Vaptans	Conivaptan, intravenous 20 mg loading dose followed by continuous infusion of 20 mg or 40 mg per day Maximum 4 days of treatment Tolvaptan, oral 15–60 mg per day (titrate in 24-hour intervals) Maximum 30 days of treatment	Rapid overcorrection of sodium (stop fluid restriction) Headache Thirst, dry mouth Liver toxicity (tolvaptan)

Modified with information from Verbalis et al. [172], Rondon-Berrios et al. [182], Hoorn et al. [181]
[a]Urine osmolality >500 mOsm/kg H_2O, 24-hour urine volume less than 1.5 L/day, urine-to-serum electrolyte ratio >1, and less than 2 mEq/L per day increase in serum sodium after 1–2 days of fluid restriction
Abbreviations: *SIADH* syndrome of inappropriate antidiuretic hormone, *mL* milliliter, *L* liter, *mg* milligram, *g* grams

The amount of fluid restriction depends on urinary output and can be guided by the urine-to-serum electrolyte ratio, which is the sum of the urine sodium and potassium divided by the serum sodium concentration [183]. This ratio reflects how the urine output may be contributing to the plasma sodium level. If the ratio is <1, the recommended fluid restriction is <1 L per day, while if it is >1, the urine is contributing more to lowering the plasma sodium so the recommended restriction is <500 mL per day [181, 183]. Predictors of failure to respond to fluid restriction include a high urine osmolality (>500 mOsm/kg H_2O), 24-hour urine volume <1.5 L per day, urine-to-serum electrolyte ratio >1, and a suboptimal response to less than 1 L per day fluid restriction (delta <2 mEq/L per day) within 1–2 days [172]. If there is inadequate response to fluid restriction, pharmacologic intervention should be considered.

While sodium chloride tablets have been used for hyponatremia to promote diuresis by increasing urinary salt load, its use alone has not been studied in clinical trials, and when it has been used, it was usually combined with a loop diuretic [182]. Previously, demeclocycline, a tetracycline derivative, that causes a nephrogenic diabetes insipidus was the preferred pharmacologic therapy for SIADH [172]. This usually took several days to work and was associated with reversible nephrotoxicity and photosensitive rash. Oral urea is another alternative treatment for SIADH that works by inducing an osmotic diuresis [181]. It has little adverse effects, though its use may be limited by its poor palatability [182]. Blood urea nitrogen levels are expected to rise and are not reflective of renal impairment [172].

The newest class of medications approved by the FDA for euvolemic hyponatremia are the vaptans, conivaptan and tolvaptan [172]. Both promote aquaresis by antagonism of vasopressin receptors in the kidney [184]. Conivaptan is a V1 and V2 receptor antagonist that is administered as a continuous intravenous infusion in the hospital. Adverse effects include headache, thirst, and hypokalemia [172, 184]. The Study of Ascending Levels of Tolvaptan in Hyponatremia (SALT-1 and SALT-2) demonstrated that tolvaptan, an oral V2 receptor antagonist, can be effectively used to treat patients with euvolemic or hypervolemic hyponatremia with [Na+] less than 125 mEq/L or less severe hyponatremia with symptoms that have not responded to fluid restriction [172, 185]. Common adverse effects included thirst, dry mouth, nausea, headache, and hypotension [185]. The Safety and Sodium Assessment of Long-Term Tolvaptan with Hyponatremia: A Year-Long, Open-Label Trial to Gain Experience Under Real-World Conditions (SALTWATER) trial was an extension of the SALT-1 and SALT-2 studies that showed that tolvaptan maintained efficacy and safety with prolonged use (median follow-up 1.7 years). Rapid overcorrection occurs more often with tolvaptan, but cases of osmotic demyelination have not been reported [184, 186].

As uncommon as the vast majority of most of the pituitary/hypothalamic hormone excess syndromes described above are, it is also important to be aware of even more rare entities of hypothalamic-pituitary hormone excess syndromes which will not be discussed in any depth in this chapter including Nelson's syndrome (aka the post-adrenalectomy pituitary adenoma syndrome) associated with excess ACTH secretion, ACTH excess syndromes associated with severe congenital adrenal hyperplasia, mineralocorticoid excess and adrenocortical hypertension secondary to pituitary adenomas overexpressing proopiomelanocortin (POMC) aka Chretien syndrome, plurihormonal pituitary adenomas including somatomammotropinomas and other complex multihormonal adenomas seen in the McCune–Albright syndrome, and other rare pituitary and hypothalamic lesions associated with over-secretion and/or cellular overexpression of various peptides including alpha-subunit, chromogranin A, ghrelin, and enterochromaffin products [187–195]. These are invariably clinically silent and not associated with discernable clinical syndromes associated with these cellular products.

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Hormone Deficiency Syndromes of the Hypothalamic-Pituitary Axis

11

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Introduction

Decreased secretion of pituitary hormones is referred to as hypopituitarism. These deficits can be partial or complete and can result from diseases of the pituitary gland itself or of the hypothalamus. The clinical presentation depends on the type of hormonal deficiency as well as the extent and severity of the deficiency. For this reason, patients can present with mild nonspecific symptoms such as fatigue or with life-threatening conditions such as profound hypothyroidism or adrenal crisis [1].

Causes of hypopituitarism can be divided into either inherited defects or acquired conditions. Inherited hypopituitarism occurs secondary to mutations in hypothalamic hormone receptors, mutations leading to pituitary structural abnormalities, or mutations leading to secretion of defective forms of pituitary hormones. Additionally, mutations in specific genes that code for multiple transcription factors have been identified as important causes of hypopituitarism (Table 11.1). Pituitary tumors are the most common cause of acquired hypopituitarism, followed by other hypothalamic and pituitary diseases such as suprasellar tumors, infiltrative disorders, radiation therapy, infection, pituitary apoplexy, and metastatic lesions. A complete list of causes of acquired hypopituitarism is described in Table 11.2. Pituitary tumors can result in hypopituitarism from mechanical compression of the normal pituitary tissue, impaired blood flow to the normal tissue, and/or interference with the delivery of regulatory hormones through the hypothalamic-hypophysial portal system. The treatment of pituitary tumors with both surgical resection and radiation can also lead to hormonal deficiencies [1, 2].

This chapter will discuss deficiency syndromes of the hormones of the hypothalamic-pituitary axis individually; however, it is important to note that these deficiencies can coexist in various combinations leading to differing presentations among patients. Deficiency of one hypothalamic-pituitary axis should alert clinicians to the possibility of loss of other axes.

Adrenocorticotropic Hormone (ACTH) Deficiency

Physiology

The hypothalamic-pituitary-adrenal (HPA) axis is one of the major systems responsible for stress and survival, and its impairment is considered a

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Table 11.1 Causes of inherited pituitary deficiency [1–3]

Receptor mutations
GHRH
CRH
GnRH
TRH
Transcription factor defects
HESX1
SOX2/3
POU1F1
IGSF1
TBX19
NR5A1
NR0B1
Hormone mutations
GH1
Bioinactive GH
FSH β
LH β
TSH β
POMC
POMC processing defect
PC1
Other genetic mutations causing hormone deficiency
NR0B1
Tpit
KAL1, FGFR1, FGF8, PROKR2, PROK2
Prop1
POU1F1 (Pit1)
Rpx, Lhx3, Lhx4, Pitx2
Structural
Pituitary aplasia
Pituitary hypoplasia
CNS masses
Encephalocele

Table 11.2 Causes of acquired pituitary deficiency [1–3]

Traumatic
Surgical resection
Radiation damage
Traumatic brain injury
Infiltrative/inflammatory
Lymphocytic hypophysitis
Granulomatous hypophysitis
Xanthomatous hypophysitis
Sarcoidosis
Histiocytosis X
Infections
Vasculitis
Hemochromatosis
Infections
Tuberculosis
Pneumocystis jirovecii infection
Fungal (histoplasmosis, aspergillosis)
Viral (cytomegalovirus)
Vascular
Pregnancy-related
Aneurysm
Apoplexy: hemorrhage into pituitary tumor, Sheehan's syndrome
Diabetes
Hypotension
Arteritis
Sickle cell disease
Pituitary tumor
Lactotroph adenoma
Somatotroph adenoma
Corticotroph adenoma
Thyrotroph adenoma
Gonadotroph adenoma
Nonfunctioning adenoma
Adenoma secreting alpha subunit
Rathke's cleft cyst
Dermoid cyst
Meningioma
Germinoma
Ependymoma
Gliomas: optic glioma, astrocytoma, oligodendroglioma, ependymoma
Craniopharyngioma
Pituitary metastases: breast, lung, colon, prostate, others
Drugs
Anabolic steroids
Glucocorticoids
GnRH agonists
Estrogen
Dopamine agonists

life-threatening condition. The HPA system is regulated by corticotropin-releasing hormone (CRH) which is produced in the hypothalamus. CRH along with other hypothalamic peptides such as vasopressin stimulate the production of proopiomelanocortin (POMC) in the anterior pituitary. POMC is a pre-prohormone molecule which is cleaved into melanocyte-stimulating hormone (MSH), endorphins, and ACTH. ACTH then acts on the cortex of the adrenal glands to induce synthesis and secretion of adrenal steroids, mainly glucocorticoids, and adrenal androgens. Mineralocorticoid production is stimulated

Table 11.2 (continued)

Somatostatin analogues
Thyroid hormone excess
Functional
Malnutrition
Excessive exercise
Critical illness
Miscellaneous
Empty sella
Internal carotid artery aneurysm

to some degree by ACTH, but it is primarily regulated by the renin-angiotensin-aldosterone (RAAS) system; thus, mineralocorticoid function is preserved in the setting of ACTH deficiency. Glucocorticoids maintain regulatory feedback control by rapidly inhibiting hypothalamic CRH and pituitary ACTH secretion. The deficiency of ACTH and CRH leads to secondary and tertiary adrenal insufficiency, respectively [2, 3].

Etiology

Inherited causes of ACTH deficiency may occur as an isolated ACTH secretion defect or as a component of a wider spectrum of multiple pituitary hormone deficiencies as described in Table 11.1. Causes of isolated ACTH deficiency include genetic causes such as mutations in proopiomelanocortin POMC gene, a cleavage enzyme defect, and mutations in the TPIT gene. Acquired causes are usually associated with other pituitary hormone deficiencies and include pituitary tumors, sellar mass lesions, trauma, irradiation, and lymphocytic hypophysitis [4]. One additional cause of ACTH deficiency is the chronic use of exogenous glucocorticoids. Glucocorticoids exert negative feedback control on the hypothalamic-pituitary-adrenal (HPA) axis by suppressing hypothalamic corticotropin-releasing hormone (CRH) production and pituitary ACTH secretion leading to adrenal atrophy and loss of cortisol secretory capability. The probability of developing HPA axis suppression will depend on the duration of treatment and doses of glucocorticoids used. Generally, any individual who has received a glucocorticoid dose equivalent to 20 mg of prednisone a day or higher for more than 3 weeks has developed ACTH suppression [5].

Clinical Manifestations

The clinical presentation of ACTH deficiency is very similar to other causes of adrenal insufficiency as clinical features are due to cortisol deficiency. Symptoms include fatigue, anorexia, nausea, vomiting, and abdominal pain. Laboratory findings include hypoglycemia and eosinophilia [6]. The most severe form of adrenal insufficiency is that of the resulting vascular collapse leading to postural hypotension, shock, and death in more severe cases. Hence, it is a condition that needs to be diagnosed and treated in a prompt manner [7].

It is important to mention that different from primary adrenal insufficiency, ACTH deficiency does not cause salt wasting or hyperkalemia as mineralocorticoid secretion is primarily regulated by the renin-angiotensin-aldosterone system (RAAS). Nonetheless, hyponatremia can be seen in secondary adrenal insufficiency due to inappropriate secretion of antidiuretic hormone (ADH) from cortisol deficiency [8]. The other main distinction between central and primary adrenal insufficiency is that patients with primary adrenal insufficiency have increased POMC synthesis which leads to elevated ACTH and MSH levels. MSH then stimulates melanocytes in the skin and produces hyperpigmentation [9].

Finally, ACTH and cortisol deficiency may cause no symptoms and no physical findings in a subgroup of patients. For this reason, prompt evaluation of the adequacy of ACTH secretion should be evaluated biochemically in all patients who have pituitary or hypothalamic disease.

Diagnosis

The diagnosis of ACTH deficiency is based on detecting low serum cortisol levels. Similar to the evaluation of adrenal insufficiency from other

causes, a serum cortisol is the first diagnostic test. Given that serum cortisol concentrations are higher in the early morning compared to the rest of the day, cortisol should be measured around 8 am. An early morning low serum cortisol concentration (less than 3 mcg/dL) is strongly suggestive of adrenal insufficiency [10]. Results should be interpreted cautiously in patients with abnormalities of cortisol-binding globulin (CBG) or albumin, such as those with cirrhosis or nephrotic syndrome or those taking oral estrogens [11]. A morning serum cortisol concentration of more than 15 mcg/dL excludes adrenal insufficiency in virtually all patients [12]. Hence, if increased CBG levels are not suspected, no further testing is required. ACTH levels are usually obtained concomitantly and are used to differentiate between adrenal and hypothalamic-pituitary causes of adrenal insufficiency. Low or normal plasma ACTH levels in the setting of a low cortisol level are indicative of secondary or tertiary adrenal insufficiency [13].

In patients with equivocal serum cortisol values (e.g., cortisol levels 3–15 mcg/dL) in whom adrenal insufficiency is suspected, dynamic testing is indicated. The initial approach is to assess the adrenocortical response to the injection of synthetic ACTH (cosyntropin). Serum cortisol is measured immediately before an intravenous (IV) or intramuscular (IM) injection of 250 mcg of cosyntropin. Serum cortisol is measured again at 30 and 60 minutes post injection. A normal response to the ACTH stimulation test is a rise in serum cortisol concentration after either 30 or 60 min to a peak of ≥18–20 mcg/dL which excludes the presence of primary adrenal insufficiency and most cases of secondary adrenal insufficiency [14]. It is worth mentioning that there may still be a detectable response to ACTH in cases of secondary adrenal insufficiency if the hypopituitarism is partial or very recent.

Other available dynamic tests include the CRH stimulation test, insulin-induced hypoglycemia, or metyrapone-induced hypocortisolemia. Since the ACTH stimulation testing is inexpensive and safe, it is the most widely used test in clinical practice [15].

Treatment

The main consequences of central adrenal insufficiency are a result of cortisol deficiency; hence, treatment consists of the administration of glucocorticoids. The appropriate dosing will depend on whether there are signs of an adrenal crisis or if patients are hemodynamically stable.

Treatment of an adrenal crisis needs to be initiated as soon as it is clinically recognized, as prolonged hypotension can lead to irremediable effects. The mainstay of management includes prompt administration of parenteral glucocorticoids such as intravenous hydrocortisone, dexamethasone, or methylprednisolone [16].

In patients without signs of adrenal crisis, glucocorticoids should be administered in a pattern that mimics the normal physiology of cortisol secretion. The cortisol circadian rhythm includes a peak in the morning and a smaller peak in the afternoon. Hydrocortisone doses ranging from 15 to 25 mg/day are equivalent to daily production rates of cortisol. Hydrocortisone doses are usually administered by dividing the total daily dose into two or three doses, with the largest dose in the morning to mimic the physiology of glucocorticoids secretion. It is also important to instruct patients to increase their glucocorticoid doses in times of illness, procedures, surgery, and other sources of stress [17–19].

Unlike replacement of other pituitary-dependent hormones, no tests exist to objectively assess the adequacy of the replacement of cortisol. Measurement of serum cortisol varies between people and is dependent on the timing of the hydrocortisone dose. Plasma ACTH levels are not useful as they are low or normal in the setting of hypopituitarism. The optimal glucocorticoid dose should then be determined by subjective means such as reported symptoms. Inadequate doses will be evidenced by the presence of persistent signs or symptoms of adrenal insufficiency. Excessive doses can lead to symptoms of cortisol excess (Cushing's syndrome) with the associated metabolic complications and bone loss [20, 21]. The goal of treatment is then to use

the lowest dose of glucocorticoids which controls symptoms to avoid the consequences of excess glucocorticoid replacement.

Thyroid-Stimulating Hormone (TSH) Deficiency

Physiology

Thyroid hormones play a critical role in infant development and normal adult physiology by affecting the function of every organ system. The hypothalamic-pituitary-thyroid system plays an important role in regulating thyroid hormone availability. About 5% of the functional anterior pituitary cells consist of the thyrotroph cells which are located in the anteromedial areas of the pituitary gland and are responsible for about 100–400 mU of thyroid-stimulating hormone (TSH) production daily. TSH is made up of an alpha subunit, which is common with luteinizing hormone (LH), follicle-stimulating hormone (FSH), and human chorionic gonadotropin (hCG), and a beta subunit, which is synthesized in thyrotrophs. Levels of alpha subunit are elevated in postmenopausal women and patients with pituitary tumors [2].

There are both pulsatile and circadian variations seen in circulating TSH levels. Pulsatile secretions are seen every 2–3 h, interspersed with non-pulsatile secretions. Circadian TSH secretion is highest between 11 pm and 5 am. Numerous factors affect TSH pulsations. Fasting, acute illness, and postsurgical stress lead to a decrease in pulsatile TSH release [2].

Etiology

Central hypothyroidism is a rare cause of hypothyroidism and occurs in about 1:20,000 to 1:80,000 people [22]. Causes of central hypothyroidism can be classified broadly into two groups: acquired and congenital. Hypothyroidism is classified as secondary when due to dysfunction of the pituitary gland and tertiary when related to hypothalamic dysfunction. In addition to the previously discussed causes of hypothalamic-pituitary hypofunction, central hypothyroidism can also be caused by bexarotene use, dopamine use, or severe illness [2]. Bexarotene (retinoid X receptor ligand) is used in the treatment of lymphoma and acts by suppressing the activity of TSH β-subunit promoter [23]. Dopamine and dopamine agonists act by inhibiting TSH secretion [24].

Congenital causes include TSH deficiency, structural abnormality of the pituitary gland or the stalk, and TSH receptor defects [2].

Clinical Manifestations

Regardless of the underlying etiology, hypothyroidism affects all organ systems, and the clinical manifestations usually depend on the degree of hormone deficiency (Table 11.3) [2].

Diagnosis

The diagnosis of central hypothyroidism should be suspected if there is known hypothalamic or pituitary disease, pituitary mass, or signs and symptoms of hypothyroidism in the setting of other confirmed or suspected pituitary hormone deficiencies. Thyroid function should be assessed by checking TSH and free thyroxine (T4) levels. In central hypothyroidism, free T4 is either low normal or low. The TSH level can vary in central hypothyroidism. It is usually low or inappropriately normal but can sometimes be slightly high (5–10 mU/L) [30]. Normal or high TSH levels occur due to secretion of TSH that has decreased biologic activity but normal immunoactivity. Normally, TSH is secreted in a diurnal rhythm with a surge late in the evening. In patients with central hypothyroidism, the diurnal rhythm is lost. Due to the loss of the late evening surge in TSH secretion, the total quantity of TSH is decreased resulting in clinical hypothyroidism [31–32].

Thyrotropin-releasing hormone (TRH) stimulation test can also be used to diagnose central hypothyroidism. This test is not available in the United States but is available in several other

Table 11.3 Clinical manifestations of hypothyroidism

Integumentary system	Increased accumulation of hyaluronic acid resulting in an edematous state [2] Easy bruising, brittle hair and nails, and decreased peripheral blood flow causing cool and pale skin [25]
Hematopoietic system	Increased risk of bleeding during a hypocoagulable state [26] Decreased production of erythropoietin due to decreased oxygen requirements, resulting in mild normocytic, normochromic anemia [2]
Cardiovascular system	Decreased cardiac output and increased peripheral vascular resistance at rest resulting in decreased blood flow to the tissues [2] Elevated total and low-density lipoprotein (LDL) cholesterol [2]
Respiratory system	Affected function of the respiratory muscles, upper airways, and tongue Depression of both the hypoxic and the hypercapnic ventilatory drives, resulting in alveolar hypoventilation and carbon dioxide retention [2]
Gastrointestinal system	Decreased gut motility resulting in constipation [2]
Reproductive system	Women Oligomenorrhea, amenorrhea, or menorrhagia [27] Men Decreased libido, erectile dysfunction, and delayed ejaculation [28]
Neurologic manifestations	Fetus Impaired neurologic development Adults Slowing of intellectual functions leading to memory defects, loss of initiative, lethargy Slow and clumsy body movements, numbness and tingling of the extremities, and slow tendon reflexes [2]
Excretory system	Decreased free water clearance resulting in hyponatremia [29] Decrease in renal blood flow and glomerular filtration rate resulting in reduced urine flow Elevated uric acid levels with preservation of blood urea nitrogen and serum creatinine levels [2]

countries. The test begins with the administration of TRH 200 mcg given intravenously. TSH is measured at baseline and then at 20 and 60 min after TRH administration. In patients without central hypothyroidism, TSH is expected to rise 5–30 mU/L from baseline at 20 min followed by a decrease in serum TSH at 60 min. However, in central hypothyroidism, there would be no serum TSH response to TRH [33].

Once central hypothyroidism is confirmed biochemically, imaging should be performed to assess the hypothalamic-pituitary region if not previously done. MRI is the preferred choice of imaging; however, if MRI is unavailable, CT scan is the next best choice [34].

Treatment

Levothyroxine is the treatment of choice for central hypothyroidism. Before starting therapy with levothyroxine, pituitary-adrenal function should be assessed to rule out adrenal insufficiency as treating hypothyroidism can unmask adrenal insufficiency and precipitate an adrenal crisis [2]. The optimal starting dose of levothyroxine is 1.6 mcg/kg, based on body weight [35]. In patients with central hypothyroidism, serum free T4 levels should be monitored as TSH is not a reliable marker of appropriate thyroid hormone replacement. The dose of levothyroxine should be adjusted based on the patient's symptoms and free T4 level. One should aim for free T4 levels in the upper normal range [36, 37].

There is not enough data to determine whether treatment with combined levothyroxine and liothyronine is superior to levothyroxine monotherapy [36]. One study showed that patients who received combined therapy had improvement in total cholesterol level and normalization of ankle reflex time but had supraphysiologic free T3 levels, which can lead to hyperthyroid symptoms such as increased heart rate, irritability, and shakiness [35, 38].

Growth Hormone (GH) Deficiency

Etiology

Causes of GH deficiency (GHD) in adults are similar to other pituitary deficiencies. These include a pituitary tumor or its treatment with surgery or radiation, craniopharyngioma, infiltrative disorders, and pituitary hemorrhage or infarction. Up to 15% of cases are idiopathic and have been associated with mutations of *PROP1* or *POU1F1* genes [2, 39].

Clinical Manifestations

Infants with GH deficiency usually manifest with hypoglycemia, prolonged jaundice, microphallus in males, and giant-cell hepatitis. Patients with GHD with onset during childhood present with severe growth failure, delayed bone age, infantile fat distribution, and underdevelopment of the nasal bridge along with frontal bossing. They also present with an infantile voice, delayed puberty, and small phallus in males. Individuals who develop GH deficiency in adulthood present with nonspecific complaints such as fatigue, lack of energy, social isolation, low mood, poor concentration, and reduced physical capacity. Body composition analysis of patients with GH deficiency shows a decrease in lean body mass and bone mineral density with an increase in fat body mass [40–42]. GH deficiency has been linked to increase cardiovascular disease and mortality [43, 44].

Diagnosis

GH deficiency in an adult individual should be suspected if there is documented pituitary or hypothalamic disease and compatible symptoms. Due to fluctuations in growth hormone level, these patients should have their serum insulin-like growth factor 1 (IGF-1) concentration measured. An IGF-1 concentration lower than the gender- and age-specific lower limit of normal in a patient who has confirmed pituitary disease establishes the diagnosis of GH deficiency [45]. If the IGF-1 value is equivocal, a subnormal serum GH response to a potent stimulus will confirm the diagnosis. Available provocative tests include an insulin-induced hypoglycemia test, an arginine and GH-releasing hormone (GHRH) test, and a macimorelin test. Other stimuli, such as arginine alone, clonidine, and L-DOPA, are weaker and therefore more likely to give false-positive results.

The insulin-induced hypoglycemia test is considered the gold standard for diagnosing GH deficiency. Normal subjects respond to insulin-induced hypoglycemia with peak GH concentrations of more than 5 μg/L [46]. However, the test has been largely replaced by the other available tests given it requires frequent supervision, is uncomfortable for the patient, and can result in severe hypoglycemia. An arginine-GHRH test is recommended in countries where GHRH is available. A bolus dose of GHRH, 1 mcg/kg body weight, is given intravenously, followed immediately by an intravenous infusion of arginine hydrochloride, 0.5 g/kg body weight (to a maximum of 30 g) over 30 min. Serum GH is measured at −30, 0, 30, 60, 90, and 120 min. The cutoff value ranges between 3.7 and 4.1 ng/dL [47]. Macimorelin is a synthetic agonist of the ghrelin receptor that stimulates GH secretion if administered orally. The macimorelin oral solution is given as a single dose of 0.5 mg/kg. GH serum levels are collected before administration and at 30, 45, 60, and 90 min after administration of macimorelin. Using 5.1 ng/mL as the cutoff point resulted in a sensitivity of 92% and a specificity of 96% [48]. Side effects of macimorelin include dysgeusia and QT prolongation; hence, discontinuation of drugs that cause QT prolongation is recommended before performing this test. A glucagon stimulation test has also been widely used. It is performed by administering 1 mg of glucagon intramuscularly (or 1.5 mg for patients who weigh >90 kg) and measuring GH every 30 min for 4 h. GH deficiency is diagnosed if GH levels are <3 ng/mL for those of normal weight, but in obese patients, a cutoff of 1 ng/mL gives the best sensitivity and specificity [49, 50].

Treatment

GH is replaced as recombinant human growth hormone administered as a daily subcutaneous injection. For children diagnosed with GH deficiency, treatment with recombinant GH is recommended at a starting dose of 20–35 mg/kg/day. IGF-1 levels should be measured at 4 weeks after starting therapy, and dose should be adjusted based on levels. Height velocity should be measured at 3- to 6-month intervals. GH therapy should be continued until linear growth is nearly complete [51].

Evidence has demonstrated that GH treatment in adults who are GH deficient results in an increase in muscle mass and a decrease in body fat with an improvement in quality of life [52]. The data on exercise capacity, bone mineral density, cardiovascular morbidity, and mortality are conflicting [53]. The data on the effect of GH treatment on mortality are limited [54]. Treatment should be offered to all patients with GH deficiency, but treatment should be individualized based on side effect profile and cost. Side effects include an increase in insulin resistance and the theoretical risk of IGF-1 acting as a growth factor in malignant cells; however, this has not been proved [55]. Other side effects include peripheral edema, arthralgias, and paresthesia [56]. Therapy should be aimed at achieving a normal IGF-1 level [57].

Follicle-Stimulating Hormone (FSH) and Luteinizing Hormone (LH) Deficiency

Physiology

Gonadotropin-releasing hormone (GnRH) signaling induces pituitary luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion by gonadotroph cells in the anterior pituitary. A pulsatile hypothalamic GnRH secretion results in stimulation of the gonadotroph, whereas continuous GnRH exposure suppresses gonadotropin secretion [2].

The primary targets of FSH and LH are the gonads, and the effects differ in male and female individuals. FSH acts on granulosa cells to facilitate follicular growth and recruitment along with estradiol biosynthesis in the ovaries. LH primarily stimulates estrogen production by promoting synthesis of androgen precursors which are subsequently aromatized into estrogens. LH also induces ovulation and induces conversion of the follicle into the corpus luteum. LH helps to sustain the corpus luteum by stimulating progesterone synthesis. In the testes, LH acts on Leydig cells to induce intratesticular testosterone synthesis. FSH acts on Sertoli cells and stimulates the production of inhibins and mediates the maturation of spermatids into spermatozoa [2, 3] .

Estrogens exert dual feedback effects on gonadotropin secretion. Negative feedback effects of estrogen are seen in elevated LH and FSH levels that follow oophorectomy or menopause, and positive feedback effects are seen in the midcycle ovulatory surge of LH and FSH secretion to induce ovulation. Progesterone decreases the frequency of GnRH pulses. Testosterone and inhibins exert negative feedback effects on gonadotropin secretion in male individuals. Nutritional, metabolic, stress, and circadian inputs all appear to modulate GnRH activity and gonadotropin secretion [2, 3].

Etiology

Inherited causes of hypogonadotropic hypogonadism associated with other hypothalamic pituitary hormonal deficits are described elsewhere. Inherited causes of isolated hypogonadotropic hypogonadism include congenital GnRH deficiency, leptin or leptin receptor mutations, gonadotropin subunit mutations, and syndromes associated with cognitive impairment (e.g., Prader-Willi). Isolated GnRH deficiency (IGD) occurs due to the functional absence of GnRH secretion from hypothalamic hypophysiotropic neurons or a defect in its action at the level of the gonadotroph in the case of mutations in the GnRH receptor. It is inherited as an autosomal

dominant or X-linked condition and can be associated with anosmia. Leptin or leptin receptor mutation syndromes present with severe early-onset obesity due to severe hyperphagia, alterations in immune function, and delayed puberty due to hypogonadotropic hypogonadism. The Prader-Willi syndrome is caused by the absence of expression of the paternally active genes of chromosome 15. It presents early in life with hypotonia and feeding problems. In older children, hyperphagia with severe obesity is the main feature along with decreased cognition and hypogonadism [58–60].

Acquired causes can be classified into conditions that suppress gonadotropin secretion and conditions that directly damage the gonadotrophs. Suppression of gonadotropin secretion is seen in hyperprolactinemia, obesity, sleep apnea, malnutrition, chronic opioid or glucocorticoid use, gonadal steroid use, and use of GnRH analogs and can also be seen in patients with critical illness or in those with chronic debilitating illnesses [61–66]. Women with eating disorders (e.g., anorexia nervosa) or women who exercise excessively who maintain a low BMI are at increased risk for functional hypothalamic amenorrhea which leads to a clinical syndrome of amenorrhea and low bone density. This occurs as conditions of low energy availability and increased stress are associated with relative hypercortisolemia and suppression of GnRH. Conditions that lead to damage of gonadotrophs are similar to other causes of hypopituitarism and include tumors, infiltrative lesions, trauma, and pituitary apoplexy.

Clinical Manifestations

Symptoms of hypogonadism in males are related to testosterone deficiency. Male patients who present prior to puberty appear younger than their chronologic age and have associated features of a delayed puberty including small genitalia, difficulty gaining muscle mass, lack of a beard, and failure of the voice to deepen. Patients with hypogonadism with onset after puberty present with somewhat nonspecific symptoms. These symptoms include fatigue, depressed mood, and loss of libido. Later in the course of the disease, patients will note decrease in muscle mass and body hair. Long-standing hypogonadism can lead to testicular atrophy and a decrease in bone mineral density. Adults may also present with gynecomastia and infertility, but this is seen less frequently when compared to primary hypogonadism [67].

Female patients who present prior to puberty present with delayed puberty, short stature, and primary amenorrhea. Postpubertal women can present with secondary amenorrhea, infertility, decreased vaginal secretion, dyspareunia, hot flashes, decreased bone density, and breast tissue atrophy [68].

Diagnosis

The diagnosis of hypogonadism in men is based upon the presence of signs and symptoms along with an unequivocally low morning serum total testosterone concentration on at least two separate occasions. The normal range in adult men in most laboratories is approximately 300–800 ng/dL. If an abnormality of the sex hormone-binding globulin (SHBG) is suspected, measurement of serum free testosterone concentration is warranted. Conditions that can increase the SHBG levels include aging, estrogens, liver disease, antiepileptics, and certain genetic mutations. Obesity, hypothyroidism, glucocorticoids, and type 2 diabetes, on the other hand, are associated with low SHBG levels [69–71]. Serum free testosterone should be performed by equilibrium dialysis and only in laboratories that specialize in endocrine testing [72]. If the serum testosterone is below normal on two occasions, a serum luteinizing hormone (LH) and follicle-stimulating hormone (FSH) concentration should be measured to distinguish primary from secondary hypogonadism. Low or inappropriately normal levels of LH and FSH indicate secondary hypogonadism.

In women with amenorrhea or oligomenorrhea, serum LH, FSH, and estradiol levels should be measured. Low estradiol levels with low or inappropriately normal LH and FSH levels indi-

cate secondary hypogonadism. Endogenous estrogen sufficiency can also be assessed by the response to a progesterone challenge (100 mg intramuscularly or 10 mg medroxyprogesterone acetate orally daily for 5–10 days). Withdrawal bleeding confirms that there has been endogenous estrogen exposure [73–75].

Management

Testosterone therapy in hypogonadal men is recommended to maintain secondary sex characteristics and correct symptoms of testosterone deficiency in patients with confirmed hypogonadism [76]. The desirable effects of testosterone administration include an increase in libido, muscle mass, and bone density. Testosterone has also been postulated to improve mood and cognition [77–79]. In men planning fertility, testosterone therapy is not recommended as it impairs spermatogenesis by suppressing pituitary gonadotropin secretion [80]. Patients who are interested in fertility should be offered human chorionic gonadotropin (hCG) as it has the biologic activity of LH but a longer half-life in the circulation and it stimulates the Leydig cells of the testes to synthesize and secrete testosterone. If the sperm count has not reached 5–10 million/mL and/or pregnancy has not occurred 6 months after serum testosterone is 400–800 ng/dL, patients should be offered the addition of human menopausal gonadotropin (hMG) which is used given the presence of an FSH extract which stimulates spermatogenesis.

Different testosterone preparations are available. Transdermal testosterone gels are usually preferred as they typically result in normal and relatively stable serum testosterone concentrations and are easy to use. Its limitations include a higher cost compared to other preparations and the potential of transfer to a female partner or child by direct skin-to-skin contact [81]. Parenteral testosterone preparations are administered as esters of testosterone which allow for a gradual release from the muscle tissue to the circulation. These preparations are inexpensive and are administered every 1–2 weeks. Limitations include fluctuating levels of testosterone and pain at the injection site. Oral preparations are available but are less effective as they are metabolized rapidly by the liver and lead to very low rates of virilization. Other less frequently used preparations include buccal tablets, subcutaneous pellets, transdermal patches, and nasal gels [76, 82].

Side effects common to all patients receiving testosterone replacement therapy (TRT) include erythrocytosis, reduced spermatogenesis, acne, and growth of androgen-dependent neoplasia. A history of prostate or breast cancer is an absolute contraindication for the use of TRT. In the presence of lower urinary tract symptoms, a palpable prostatic nodule on exam, or a PSA >4 ng/dL or >3 ng/dL in high-risk populations, patients should have a urological evaluation prior to TRT. A hematocrit of >48% also warrants further evaluation prior to TRT [76, 83]. Another risk related to TRT has been its increased risk for venous thromboembolism (VTE) unrelated to the presence of polycythemia. It is important to screen patients for a family or personal history of VTE prior to starting therapy, and risks and benefits should be discussed. There are also potential concerns about testosterone therapy and cardiovascular safety. Despite conflicting evidence, there is a possibility of increased cardiovascular risk associated with testosterone use. Risks regarding the possibility of increased risks of myocardial infarctions (MIs) and strokes in patients taking testosterone should be discussed with patients prior to initiation of therapy [84].

Premenopausal women with hypogonadism due to pituitary disease who are not interested in fertility should be treated with estradiol replacement therapy. The goal of treatment for postmenopausal women is to give estradiol only if necessary to relieve hot flashes. Women with an intact uterus must also take a progestin to avoid the risk of endometrial hyperplasia or carcinoma. Women with secondary hypogonadism who wish to become fertile should be offered ovulation induction with gonadotropins [85]. It should be noted that some conventional fertility treatments

such as clomiphene citrate, letrozole, and leuprolide trigger injections are dependent on normal gonadotroph function and thus may not be effective in treating infertility due to hypogonadotropic hypogonadism.

Prolactin Deficiency

Etiology

Prolactin deficiency typically occurs in combination with other pituitary hormone deficiencies although there are case reports describing isolated prolactin deficiency in women [86, 87] but not in men. Congenital prolactin deficiency has also been noted due to mutations in the transcription factors associated with lactotroph development [2].

Clinical Features

Women have difficulty with lactation and reproduction as a result of prolactin deficiency [2].

Treatment

There is no commercially available prolactin preparation [2]. Recombinant human prolactin is currently under clinical trial [88].

Antidiuretic Hormone (ADH) Deficiency

Physiology

Antidiuretic hormone (ADH), also known as arginine vasopressin (AVP), is primarily synthesized in the hypothalamus. The hormone is then transported through the hypothalamic-hypophysial tract where it is released in the posterior pituitary gland, before entering the systemic circulation [89]. Vasopressin acts on the V2 receptors in the distal renal tubule and collecting duct to promote water reabsorption in the kidneys and acts on V1 receptors on the blood vessels to control blood pressure [3].

A decrease in the release of ADH causes a condition known as central diabetes insipidus, resulting in polyuria. It usually occurs when one or more sites of ADH synthesis are affected. The primary sites include the hypothalamic osmoreceptors, the supraoptic or paraventricular nuclei, or the superior portion of the supraopticohypophyseal tract [90]. As ADH produced in the hypothalamus can also be secreted into the systemic circulation through the capillaries in the median eminence, any damage to the hypothalamic-hypophysial tract below the median eminence or to the posterior pituitary gland causes transient polyuria [90].

Etiology

The causes of central diabetes insipidus (CDI) can be broadly classified as the following: idiopathic, familial and congenital, postsurgical, traumatic, or secondary to another disease process [2]. CDI can also develop during or be exacerbated by pregnancy due to increased production of vasopressinases from the placenta, leading to increased catabolism of ADH [91, 92].

Familial and congenital causes of CDI include familial CDI, Wolfram syndrome, congenital hypopituitarism, and congenital cerebral midline abnormalities [93]. Familial CDI is caused by mutations in the gene encoding ADH. It is also known as familial neurohypophyseal DI (FNDI) [92]. Although it is usually autosomal dominant, there have been case reports of autosomal recessive FNDI [94]. Both types vary in terms of onset and progression. The autosomal dominant form typically has a delayed onset, whereas those with autosomal recessive FNDI have an early onset [94, 95]. Wolfram syndrome, which occurs due to loss of vasopressin-secreting neurons in the supraoptic nucleus and defective processing of vasopressin precursors, is inherited as an autosomal recessive trait with incomplete penetrance. It is characterized by diabetes mellitus, CDI, optic nerve atrophy, vision loss, hearing impairment, motor abnormalities, and neurodegeneration [96, 97].

Neurosurgery or trauma to the hypothalamus or posterior pituitary can cause CDI [98, 99]. A retrospective study conducted between 1995 and 2001 at the University of Virginia Health System showed 18.3% developed immediate post-op DI and 2% progressing to permanent DI [100].

Finally, CDI can develop as the result of underlying disease processes including malignancy [101], hypoxic encephalopathy, infiltrative disorders, and anorexia nervosa. Common malignancies affecting the hypothalamic-pituitary region include craniopharyngioma, primary germ cell tumors, and metastatic tumors (usually lung cancer, leukemia, or lymphoma) [2]. Hypoxic encephalopathy or severe ischemia following cardiopulmonary arrest or shock can result in decreased ADH secretion, thus causing CDI [90, 102]. Infiltrative disorders causing CDI due to hypothalamic-pituitary involvement include Langerhans cell histiocytosis, sarcoidosis, granulomatosis with polyangiitis, and autoimmune lymphocytic hypophysitis [103–106]. A transient decrease in ADH secretion can also be seen following episodes of supraventricular tachycardia [107]. Those with anorexia nervosa have subnormal decrease in ADH production, which is believed to be due to cerebral dysfunction [108].

Clinical Manifestations

Central diabetes insipidus usually presents with an abrupt onset of polyuria and polydipsia. The serum sodium is usually in the high normal range, which is necessary to stimulate the thirst center. Severe hypernatremia can occur when the thirst center is impaired or if patients do not have access to water or the ability to drink to compensate for free water losses [2]. It has also been noted that patients with CDI have decreased bone density in the lumbar spine and femoral neck. Although the mechanism of CDI causing osteoporosis is unclear, it has been hypothesized that ADH induces production of prostaglandins, which in turn are involved in bone metabolism [109].

Diagnosis

The first step in diagnosing CDI is to confirm polyuria. Polyuria has been defined as urine output of more than 3 liters in 24 h. Obvious causes of polyuria should be ruled out with a thorough history and focused laboratory testing before more comprehensive evaluation. Some of these include primary polydipsia, uncontrolled diabetes mellitus with glucosuria, treatment with SGLT-2 inhibitors, treatment with exogenous urea or glucocorticoids, consumption of a very high-protein diet, administration of large volumes of saline, release of bilateral urinary tract obstruction, and administration of mannitol to patients with elevated intracranial pressure [110–114].

Once these causes have been excluded, the next step is to measure 24-hour urine creatinine, sodium, potassium, chloride, urea nitrogen, and glucose. However, if 24-hour urine collection is not possible, spot urine measurements of sodium, potassium, chloride, urea nitrogen, and glucose can be used. Along with the abovementioned labs, urine osmolality, plasma electrolytes, serum glucose, and renal function should be checked [115].

A normal serum sodium level along with urine osmolality less than 300 mosmol/kg is suggestive of either primary polydipsia or diabetes insipidus (central or nephrogenic). A normal serum sodium level along with urine osmolality level between 300 and 600 mosmol/kg could be due to solute diuresis, primary polydipsia, or diabetes insipidus (central or nephrogenic). To distinguish between primary polydipsia and diabetes insipidus, a water deprivation test can be done. Patient is restricted of fluids for 8 h or until 5% of the body mass is lost. Body weight, plasma osmolality, urine volume, and osmolality are checked intermittently. A high urine osmolality (>800 mosmol/kg) excludes DI. For those with lower urine osmolality (<800 mosmol/kg), 2 mcg of desmopressin is administered intramuscularly, and plasma and urine osmolality are measured. In those with CDI, the urine osmolality is <300 mosmol/kg before administration of desmopressin and increases to >800 mosmol/kg afterward [115, 116].

Treatment

The preferred choice of therapy for central diabetes insipidus is desmopressin. It is recommended to start with the minimum dose possible to control polyuria and then increase the dose as needed based on symptoms. The first dose should be given at bedtime to decrease nocturia. The daytime dose, if needed, can be determined based on when the patient has polyuria during the day [117].

Once therapy is initiated, serum sodium level should be monitored closely as there is an increased risk of developing hyponatremia [117]. Thus, it is recommended that the serum sodium level is monitored closely; it should be checked 1–2 days after starting desmopressin; if normal, then repeat it again after 4 days. Once a stable dose of desmopressin is achieved, then serum sodium level can be followed once a year [118, 119].

Desmopressin can be administered in multiple ways: intranasal, oral, sublingual, subcutaneous, and intravenous [120]. The choice of route of administration should be based on the clinical scenario, patient preference and response to treatment, and cost.

Studies have shown that when chlorpropamide and carbamazepine are used in combination for treatment of CDI, there is an increased antidiuretic effect. Other therapy options include NSAIDs, thiazide diuretics, and low-solute (low salt, low protein) diet. Low-solute load along with thiazide diuretics can help achieve eunatremia, especially in infants. In adults, desmopressin is considered the first choice of treatment for CDI due its effectiveness and lower side effects when compared with other medications [121–123].

Conclusion

Despite the etiology, hypopituitarism is treatable with the goal of therapy to be replacement of the deficient hormone(s). The secretion of gonadotropins and GH is more commonly affected than that of ACTH and TSH. However, there are many exceptions, and thus, patients should undergo a thorough evaluation to determine the type of hormonal deficiency as well as the extent and severity of the deficiency so that the proper replacement regimen can be determined. Improper hormone replacement can affect the quality of life. Specifically, cortisol and thyroxine are essential for life, and a lack of replacement can result in death. Lack of sex steroid replacement leads to infertility in premenopausal women and increases the risk of osteoporosis. Improper replacement of vasopressin causes polyuria and polydipsia, thus resulting in hypovolemia and hypernatremia [1]. A retrospective study that examined 333 patients with hypopituitarism diagnosed between 1956 and 1987 showed that these patients are at an increased risk for cardiovascular disease, most likely due to deficient growth hormone and estrogen deficiency in women [124]. Once a proper replacement regimen has been determined, it is important to educate patients about taking hormonal replacement therapy on a regular basis and the need to increase the dose of steroids during illness.

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Hypothalamic Obesity and Wasting Syndromes

12

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Introduction

Hypothalamic disease or dysfunction has been appreciated to cause phenotypes of morbid obesity and less commonly wasting cachectic syndromes since the classic lesional and electric stimulation experiments of Hetherington and Ranson [1]. These experiments showed the capacity to induce obesity from localized lesions of the ventromedial nucleus (VMN) in rats and have since been replicated in other animal models. Contrawise, bilateral lesions of the lateral hypothalamus in similar animal models resulted in a wasting syndrome, and based on these and similar animal experiments, the concepts of a VMN-based "satiety center" and a lateral hypothalamic area (LHA)-based "hunger" or "feeding" center as central hypothalamic determinants of weight regulation in animals became established and popular. Clinical observations in humans pointed to similar clinical phenotypes associated with variable hypothalamic and pituitary-based lesions including observations from Reeves and Plum of morbid obesity with hyperphagia in a young woman with a hamartoma involving the VMN [2].

Other clinical observations in clinical medicine in the following decades added to the evidence of a distinct hypothalamic obesity syndrome (HOS) and hypothalamic wasting syndrome (HWS) of variable etiologies. Babinski and Frohlich described cases of HOS induced by hypothalamic tumors including the initial description of the Frohlich's syndrome characterized by pediatric-onset morbid obesity and hypogonadism [3–5]. Other reports detailed wasting syndrome related to hypophyseal lesions both in animals and humans including the classic descriptions of Simmonds' cachexia [6–12].

The increasing appreciation of HOS in patients with the Prader-Willi syndrome and craniopharyngiomas in the following decades increased the visibility of this phenotype and its recognition as a unique clinical entity [13–18]. At this stage in understanding of HOS and HWS, hyperphagia versus profound anorexia were presumed to be the major determinants of the clinical phenotypes however understanding of the anatomic, cellular and molecular basis of the syndromes were still rather vestigial. As neuroanatomic characterization of HOS improved, it became clear that while hyperphagia was often a component of the syndrome, it was not required nor universal for the development of the condition [19–21]. This period of growth in understanding of HOS in particular

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also included a growing appreciation of the additional metabolic and dysautonomic features often associated with it, and it is also now appreciated to often coexist in patients with HWS [19, 22].

The next epochal development in the understanding of both HOS and HWS was the isolation of leptin by Friedman and colleagues which began the neurohormonal era of hypothalamic dysfunction syndromes related to weight and energy balance while also beginning the better appreciation of the roles that adipocytokines, enterocytokines, and other peripherally derived signal molecules have on hypothalamic regulation of satiety, caloric intake, and energy balance [23].

While HOS and HWS have been traditionally presumed to be rare clinical syndromes, it is now emerging that these conditions are significantly more common than previously thought. In addition, they tend to be particularly treatment resistant compared to non-hypothalamic obesity and wasting syndromes. The etiology of these syndromes is quite variable but does provide a unique insight into various aspects of hypothalamic weight management and energy balance, as well as providing information for new innovative therapeutic strategies to modulate this in clinical settings. As further detailed below, the causes of HOS and HWS involve lesions that affect various hypothalamic nuclei including traumatic lesions, neoplastic and mass lesions, inflammatory and infective lesions, post-neurosurgical effects (particularly from posterior fossa surgical procedures), syndromes associated with increased intracranial pressure, and myriad genetic syndromes [7, 8, 12, 16, 24–28]. While these syndromes have been described with lesions spanning the entirety of the hypothalamus, the obesity-related syndromes are clearly more prevalent than the wasting ones, and lesions of the VMN, paraventricular nucleus (PVN), and/or the amygdala are most commonly implicated for reasons that become clearer in the discussion below regarding the hypothalamic modulation of caloric intake, satiety, and energy balance [28–33].

A commonality of these conditions is the common association of the clinical presentations with other features of hypothalamic and pituitary dysfunction which will be described in more detail below. Some features seen in association with both HOS and HWS include symptoms of increased intracranial pressure including headaches and impaired vision; symptoms of endocrinopathies including but not restricted to hypogonadism (or occasionally hypersexuality), diabetes insipidus, and growth retardation; and other neurologic and neurobehavioral symptoms such as seizures, altered levels of consciousness ranging from somnolence to coma, and the full range of possible neuropsychiatric syndromes [24, 34, 35].

Overview of Hypothalamic Regulation of Appetite, Satiety, and Energy Expenditure

It is now known that both the rare monogenic and the more common polygenic forms of obesity are determined by a variety of *genes* which are richly expressed in the hypothalamus. Better understanding of these genes, their products, and the effects they cause added to toe initial lesional and stimulation experiments of Hetherington, Ranson, and others has provided a more complete picture of hypothalamic modulation of appetite, satiety, feeding behavior, and energy balance. In addition to this though, the hypothalamus is intricately involved in endocrine system modulation; salt, water, and intravascular volume control; body temperature regulation; sleep and wake cycle modulation; circadian and circannual rhythm coordination; sexual and reproductive function including modulation of menstrual cycling, pregnancy, lactation, and other related behavior; emotional behavioral responses; environmental stress and adaptive responses; and general modulation of metabolism, all of which can become dysregulated when the weight regulatory functions of the hypothalamus become dysfunctional [36–44]. While the original concept of the VMH as the "satiety center" and the lateral hypothalamic area as the "feeding center" serves as a helpful concept in the early days of hypothalamic neuroendocrinology, it is now obvious that this concept is oversimplistic

especially in humans as opposed to rodents [22, 45–47].

The hypothalamus mediates its modulatory effects on energy balance, satiety, and food intake by receiving a host of afferent neuronal inputs from the rest of the body and other parts of the central nervous system including other parts of the hypothalamus. In addition, various hormones and other circulating chemical mediators from various systemic tissues including the gastrointestinal tract, adipocytes (white, brown, and beige), liver, pancreas, and skeletal muscle among others also influence the hypothalamus' modulatory function on energy balance, satiety, and feeding behavior [48–50].

Leptin was the first of a panoply of such peripherally derived signals that is now recognized to mediate its effect on energy balance via the hypothalamus. Leptin in particular serves as a "fat sensor" that indicates by central signaling the adequacy of fat stores in the organism. It mediates behavioral, metabolic, and neuroendocrine adaptations related to nutrient and energy balance [51–58]. In settings of caloric and energy excess with associated adequate adipose tissue stores, leptin secretion is reduced and via its central signaling in hypothalamic nuclei results in reduced appetite (anorexigenic effect) and increased energy expenditure, while in settings of caloric and energy deficit with depleted adipose tissue stores, leptin secretion decreases with opposite effects at the level of the hypothalamus to those previously detailed [59–62].

The major site of action of leptin in the hypothalamus is the mediobasal hypothalamus in the arcuate nucleus (AN), and it mediates the majority of its central nervous system activity by activation of specific leptin receptors, the OB receptor (Ob-R), which has dichotomous effects on two major subgroups of neurons within the AN with oppositional functions. Among the signaling pathways involved in the activation of these groups of neurons by leptin are the Jak-STAT, PI3k-Akt-FoxO1, SHP2-ERK, AMPK, and mTOR-S6k pathways [63–65]. There are two major groups of these neurons in the AN, one that co-expresses the cocaine-associated receptor transcript (CART) and alpha melanocyte-stimulating hormone (α-MSH) and a second that co-expresses the agouti gene-related peptide (AGRP) and a neuropeptide Y (NPY). These two sets of neurons constitute the main anorexigenic (satiety) and orexigenic (feeding) mediating centers of the hypothalamus [66]. Projections from these neurons extend to other hypothalamic nuclei as well as to other parts of the brain involved in feeding activity, energy expenditure, and pituitary function [51, 52, 55, 57]. Reduction in serum leptin levels that occurs, for example, with fasting and states associated with reduced adipose stores (such as significant weight loss including wasting states and cachexia) results in simultaneous reduction in the production of various chemical signals, mediators, and hormones that promote satiety and increased energy expenditure of which α-MSH and CART are two prime (but not the only) products. In addition, concomitantly, the production of chemical mediators associated with promoting caloric intake and reduced energy expenditure is increased, of which AGRP and NPY are prime (but not exclusive) mediators.

Table 12.1 provides a listing of the main chemical mediators involved in the anorexigenic and orexigenic effects of various hypothalamic nuclei.

The two sets of neuronal nuclei have complementary negative feedback effects on each other, thus providing another level of regulation of this intricately balanced system. AGRP secreting hypothalamic nuclei, for example, have been shown to have competitive antagonistic action on α-MSH and POMC expression that is mediated by inhibition of the melanocortin 3 and 4 receptors (MCR-3 and MCR-4) by which these mediators achieve their effects [56, 67]. Of these two systems of balance, the melanocortin signaling system appears to be dominant modulatory network. This is suggested by the fact that animal models with isolated NPY deficiency have normal phenotypes with appropriate caloric response to fasting, while those with isolated functional MCR-4 defects result in severe obesity syndromes. There are also well-described human equivalents of MCR-4 *gene* mutations, POMC mutations, and mutations of the proconvertase

Table 12.1 List of chemical mediators of hypothalamic modulation of satiety, appetite, feeding, and energy expenditure

Neuropeptides and other hypothalamic chemical mediators that modulate feeding, satiety, energy expenditure, and related behavior	
Orexigenic factors	Anorexigenic factors
Ghrelin	Leptin
NPY	α-, β-, and ϒ-MSH
AGRP	POMC
Orexins A and B	CART
Melanocyte-concentrating hormone (MCH)	CCK
Insulin[a]	Insulin[a]
Galanin	GLP-1
Pancreatic polypeptide	Amylin
Thyroid hormone; LT4 and LT3	Oxyntomodulin
Adiponectin	PYY
Endocannabinoids (ECBs)	Obestatin
Dopamine	Nesfatin-1
Serum hypoglycemia	Bile acids
	Serotonin (5HT)
	Free fatty acids (FFA)
	L-leucine

[a]Insulin's effect on feeding behavior is variable depending on the route and location of exposure with capacity to induce both orexigenic and anorexigenic feeding responses. The orexigenic response invariably occurs in the setting of associated consequent hypoglycemia

processing enzyme that all lead to unique monogenic obesity syndromes [68–72]. In essence thus, the hypothalamic regulatory system is intrinsically more attuned to defend against wasting and maintenance of adequate body weight. Consequently, HWSs are significantly less common than HOSs, and it typically requires more extensive and often multiple hypothalamic lesions to cause HWS, while discrete single lesional/genetic defects are well known to cause HOS. It also appears that age-related loss of neuronal tone in the AN POMC secretory neurons may be one major contributor to the typical age-related progressive weight gain [73, 74]. Furthermore, melanocortin receptor antagonists have been shown to prevent development of cancer-related cachexia in animal models [75, 76]. The AN neuronal projections to the paraventricular nucleus of the hypothalamus (PVN) play an important functional role in the modulation of feeding behavior and energy expenditure by thyroid hormone action. TRH-producing neurons from the medial parvicellular PVN receive projections from both the α-MSH/CART-producing and the AGRP/NPY-producing neurons of the AN, thus modulating the effect of systemic thyroid hormone on TRH production and secretion [77–80]. From the PVN, there are projections to the limbic system, brain stem, spinal cord, and other components of the autonomic nervous system (ANS). There is also evidence indicating that PVN projections are also involved in modulating brown adipose tissue (BAT) expression and function including effects on uncoupling protein 1 (UCP1) [81, 82].

An important relay station for the PVN downward projections is the brain stem-located parabrachial nucleus which is involved in appetite suppression. Projections from the parabrachial nucleus include the amygdala with calcitonin gene-related peptide (CGRP) as a prominent neurotransmitter involved [83, 84]. Other PVN-located neurons serve as central sensory signal stations for various bowel-derived satiety signals such as cholecystokinin (CCK), and oxytocin is a prominent neurosecretory product of these cells [85–89].

Beyond the PVN, other important hypothalamic relay stations for AN-derived neuronal projections are two distinct neuronal populations in the lateral hypothalamus which are melanocyte-concentrating hormone (MCH) and orexin [90]. From the lateral hypothalamus, these neurons then project to various other locations including the cerebral neocortex, midbrain, pons Varolii including the ventral tegmental area (VTA), and the nucleus accumbens (NA) which is well established as the main reward center associated with hedonic and addictive eating behavior [91, 92]. While MCH is a standard orexigen that stimulates caloric intake, orexin despite its name is more involved in arousal responses with increased food intake as a less prominent secondary effect in addition to increased gastric contractility [92–97]. In settings of caloric restriction and lack, the orexin- and MCH-producing lateral hypothalamic neurons are activated and inhibit satiety

signaling mediated via the vagus nerve, stimulate increased caloric intake, and induce weight gain in the long term [98]. Leptin response CART-producing neurons from the AN also project to the intermediolateral cellular column of the spinal cord, and this serves as one of the neuronal projections by which feeding behavior and energy balance modulate autonomic control and function [99].

Beyond the AN, leptin's CNS action is mediated by other hypothalamic nuclei with leptin receptor expression including portions of the dorsomedial nucleus (DMN) and the ventromedial nucleus (VMN) [51, 93, 100]. The DMN has extensive neuronal projections to the PVN (especially portions of it associated with ANS modulation) and the dorsomotor complex of the vagus nerve in the brain stem [101]. The DMN also receives rich afferent input projections from the α-MSH/CART and AGRP/NPY-producing neurons from the AN [102, 103]. The DMN clearly plays a central role in the homeostatic control of caloric intake as lesions of it in animal models result in a phenotype of hypophagia and reduced linear growth though not of gross cachexia. Among other effects, it may mediate the anorexigenic effects of CCK-8 secreted by neurons projecting to it from the parabrachial nucleus [104–106]. The leptin-responsive VMN neurons also have a role in appetite and feeding behavior as well as in regulation of circadian rhythms [51, 93, 100, 104–106].

The dorsal vagal nuclear complex (DVNC) is the major brain stem relay station with leptin-responsive neurons involved in caloric intake [107]. It receives visceral afferent signaling via the vagus nerve from the gastrointestinal tract but also receives afferent inputs from portions of the forebrain including the PVN [57]. Some of the leptin-responsive neurons of the DVNC produce glucagon-like peptide 1 (GLP-1) which is anorexigenic. These neurons project among other targets to the NPY-producing neurons of the AN where GLP-1 exerts an inhibitory effect [108–111]. These GLP-1 projecting neurons from the DVNC also project to the PVN and DMN where they also mediate anorexigenic effects [112, 113]. Leptin has enhancing effects on the anorexigenic effects of CCK-producing neurons in the DVNC and dopaminergic neurons in the ventral tegmental area (VTA).

In addition to leptin, there are also a number of bowel-derived peptides that have modulatory effects on appetite and satiety. Most of these mediate their effects either via direct action on the AN or via the vagus nerve on the DVNC [114–116].

Table 12.2 provides a listing of some of the most well-characterized peptide products of this brain-enteric axis of satiety and appetite regulation as well as other peripherally derived centrally acting chemical mediators of satiety, appetite, and energy balance.

Insulin has a complex relationship and effect in this regard as its secretion from the pancreatic beta cells is reduced with caloric intake but increased with fasting states. Centrally administered in the ventricular system of the brain, insulin has anorexigenic properties mediated among other routes by reduction in the firing of the AN-producing NPY and AGRP orexigenic neurons. Peripherally and systemically on the other hand especially when secreted chronically and associated with hypoglycemia, insulin is in contradistinction associated with orexigenic effects.

Amylin which is co-secreted with insulin from the pancreatic beta cells in response to caloric intake has anorexigenic effects that are mediated via central effects on serotonin (5-hydroxytryptamine; 5HT), dopamine, and histamine CNS release [117]. CCK and peptide YY (PYY) are secreted from the intestines in response to caloric intake and mediate anorexigenic effects. CCK mediates its effects via central vagal afferents, while PYY acts centrally via the Y2 receptors of the AN-located NPY and AGRP secretory neurons [118–123].

In addition to GLP-1's central production and effects highlighted above, it is also produced peripherally from the distal jejunum ileum and the colon in response to caloric intake. It has an anorectic effect which is then mediated by central direct actions detailed above as well as via afferent inputs from the vagus nerve.

Oxyntomodulin is another anorexigenic gut-derived peptide and is largely produced from the

Table 12.2 Systemic mediators of hypothalamic regulation of appetite, satiety, and energy balance

Systemic chemical mediators of hypothalamic satiety, appetite, energy expenditure, and weight modulation					
Orexigenic factor	Chemical type	Source	Anorexigenic factor	Chemical type	Source
Insulin[a]	Peptide	Pancreas	Leptin	Peptide	Adipose tissue
Ghrelin	Peptide	Stomach	Insulin[a]	Peptide	Pancreas
T3 and T4	Bioamines	Thyroid gland	Amylin	Peptide	Pancreas
Adiponectin	Peptide	Adipose tissue	CCK	Peptide	Intestines
Endocannabinoids	Fatty acid derivatives	Variable	PYY	Peptide	Intestines
Gut microbiota products	Variable	Intestines	GLP-1	Peptide	Intestines
			Oxyntomodulin	Peptide	Intestines
			Pancreatic polypeptide	Peptide	Pancreas
			Obestatin	Peptide	Stomach
			Nesfatin-1	Peptide	Stomach
			Bile acids	Fatty acid derivatives	Biliary system
			Gut microbiota products	Variable	Intestines

[a]Insulin's variable effects are due to differential effects when acting centrally vs peripherally and with or without associated hypoglycemia

same locations and cells that produce GLP-1. It is produced by posttranslational modification and processing of proglucagon and has similar actions to GLP-1 that are mediated via the same GLP-1 receptor. In addition and distinct from GLP-1, however, it also appears to have positive modulatory effects on energy expenditure [124].

Pancreatic polypeptide (PP) is another secretory peptide product of the pancreatic endocrine islets and has anorexigenic effects mediated by acting centrally on the Y4 receptors on neurons in the DNVC as well as on neurons of the AN via vagal afferent inputs [125].

Ghrelin is produced mainly from the stomach wall lining endocrine cells and is secreted into the systemic circulation in typical endocrine fashion but distinct from the prior mentioned peptides has an orexigenic effect. Its production is increased in fasting states and reduced with caloric intake [126]. Ghrelin's effects centrally are mediated at the AN on the NPY-/AGRP-secreting neurons which it stimulates while concomitantly inhibiting the action of the anorexigenic POMC neurons that produce α-MSH and CART. There is also evidence that ghrelin has some vagally mediated effects [126–129]. There is also some suggestion that hyperproduction of ghrelin may be one of the pathophysiologic mechanisms underlying the morbid obesity associated with the Prader-Willi syndrome [130]. The fact that therapy with somatostatin which inhibits ghrelin production does not significantly impact the obesity nor hyperphagia associated with Prader-Willi syndrome however emphasizes that ghrelin overproduction is certainly not the only etiologic mechanism for the observed clinical phenotype [131–133].

Another gastric-derived peptide of note is obestatin which is another posttranslational product of the ghrelin *gene*. While its full role in energy balance and appetite modulation is not fully understood yet, it does appear to have anorexigenic effects in contradistinction to ghrelin [134]. Another gastric-derived peptide which appears to co-localize with ghrelin is nesfatin-1 which also has satiety-inducing properties. Nesfatin-1 production also occurs locally in the lateral hypothalamus and the PVN [135–138]. There is also increasing evidence that products from the bowel microbiota and bile acids also have centrally mediated effects on energy balance as well as satiety and appetite balance [114,

139]. While the full details of the mechanisms of action are still not fully elucidated, it does appear that various bioactive chemical mediators produced by bowel microbiota including short-chain fatty acids, bile acids, methylamines, amino acid metabolites, lipopolysaccharides, etc., mediate various effects of appetite and satiety regulation as well as energy balance and that these are mediated by action on hypothalamic nuclei as well as peripherally [140–145]. The bile acids in particular mediate their effects via action on the farnesoid X receptor (FXR) and the Takeda G protein-coupled receptor-5 (TGR5) and have become the object of intense investigation to develop designer bile acids that can exploit and accentuate the established anorexigenic and increased energy expenditure-inducing properties of several endogenous bile acids for obesity therapeutics [142].

Thyroid hormone also appears to play a role in energy balance and satiety/appetite regulation. Hyperthyroid and thyrotoxic clinical states are well known to be associated with hyperphagia. Some of this clinical effect is mediated via central effects of both thyroxine (T4) and liothyronine (T3) on hypothalamic nuclei including the NPY-producing neurons of the AN and in the VMN [146–151]. The hypothalamus in particular has been shown to be associated with rich thyroid hormone receptor expression. Systemically administered doses of T4 and T3 are associated with hypothalamic-mediated increases in caloric intake.

Other than leptin, it is now appreciated that other adipose-derived peptides and other chemical mediators (adipokines) also modulate appetite, satiety, and energy expenditure [152, 153]. One of the major adipokines in this regard is adiponectin (aka GBP-28, apM1, AdipoQ, and Acrp30) which acts primarily as a starvation chemical signal in contradistinction to leptin that functions primarily as a satiety chemical signal.

Its major CNS-mediated actions are mediated via the adiponectin-1 receptors in the AN and by activating AMP kinase activity with the end result of increased caloric intake and reduced energy expenditure. It also acts peripherally by reducing uncoupling protein-1 (UCP-1) activity in the brown adipose tissue (BAT) [154].

The hypothalamic regulation of energy balance and caloric intake is also modulated by the effects of endocannabinoids and the endocannabinoid system (ECS) as well as by the effects of exogenous exposure to cannabidiol and related phytochemicals [155–161].

The cannabinoid 1 (CB1) receptor is the main cannabinoid receptor expressed in the CNS and has been demonstrated to be widely distributed in the hypothalamus and the limbic system [162, 163]. The main endogenous cannabinoids are anandamide and 2-arachidonoyl glycerol (2-AG). They have orexigenic effects that appear to be mediated via ghrelin, stimulating melanocyte-concentrating hormone (MCH) release in the lateral hypothalamic area and reducing the activity of anorexigenic neurons from the PVN [164, 165]. In addition, the endocannabinoids stimulate the mesolimbic dopaminergic system that is involved in hedonistic eating behavior.

The ECS is a systemic network that is present throughout the body in multiple tissues and organ systems including the hypothalamus and the rest of the CNS. Chief among the nonneuronal components of the ECS are the adipose tissue ECS, the hepatic ECS, the gastroenteric ECS, the pancreatic ECS, and the skeletal muscular ECS [155, 156, 159]. In addition, the immunomodulatory cells and various endocrine organs including the pituitary, ovaries, testicles, placenta, and thyroid all express ECB receptors as well.

The ECS also consists of CB1 and cannabinoid 2 (CB2) receptors which are widely distributed and the endogenous cannabinoids, anandamide, and 2-AG (aka the endocannabinoids; ECBs). Other less well-characterized ECBs have also been identified including noladin ether, virodhamine, N-arachidonoyl dopamine (NADA) and oleoylethanolamine (OEA). All the ECBs are derivatives of omega-6 polyunsaturated fatty acids (especially arachidonic acid) and membrane-derived phospholipid precursors.

Figure 12.1 is a schematic representation of the role of ECBs and ECS in hypothalamic and other CNS regulation of caloric intake and satiety, while Fig. 12.2 shows the major biosynthetic and degradation pathways for the main two ECBs. Figure 12.3 details the relative systemic

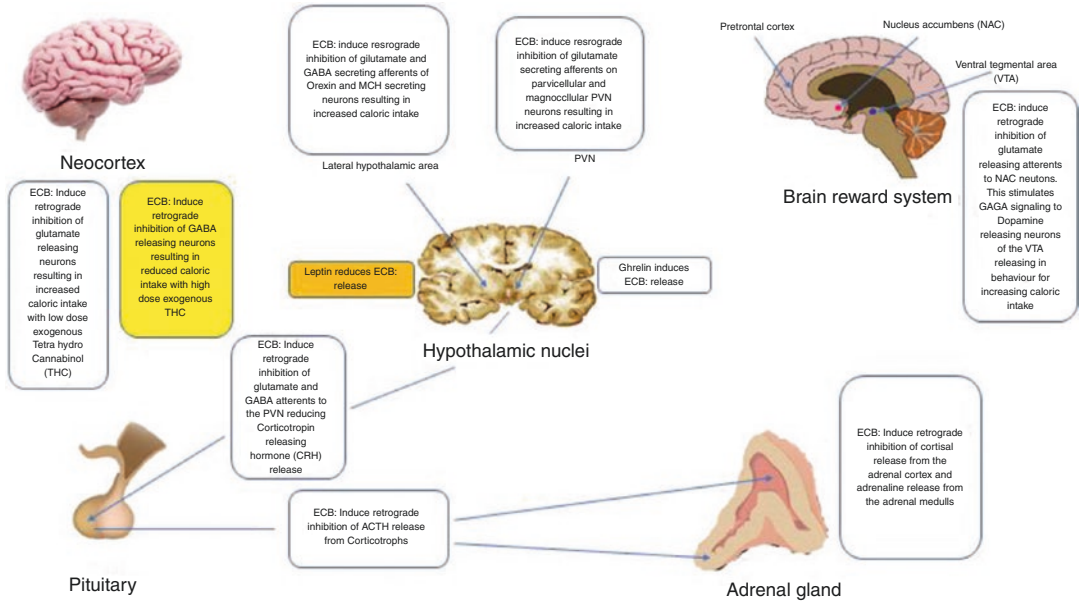

Fig. 12.1 Schema of endocannabinoid regulation of hypothalamic and CNS appetite and satiety signaling

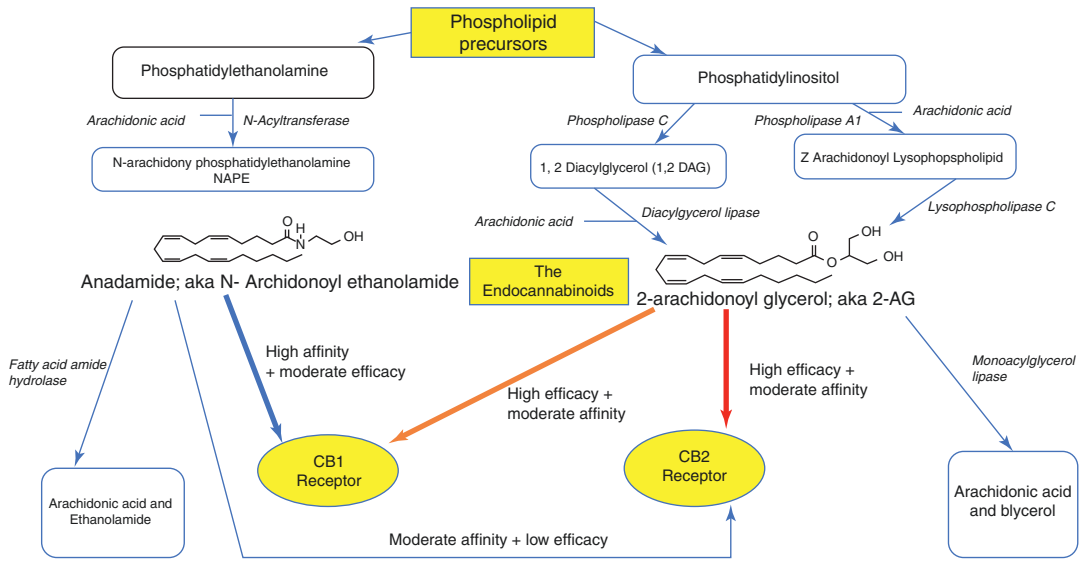

Fig. 12.2 Endocannabinoid metabolism; biosynthesis, degradation, and action

distributions of the CB1 and CB2 receptors in the body.

Centrally acting neurotransmitters also play a crucial role in the modulation of caloric intake and energy balance. GABA appears to be central to the orexigenic effects of the AGRP-producing neurons of the hypothalamus as the selective central inhibition of its action results in a lean phenotype even with high fat-containing caloric intake [166]. Furthermore, selective removal of leptin receptors from GABA-expressing neurons results in profound hyperphagia and an obese phenotype [167].

Serotonin (5HT) is another centrally acting neurotransmitter with profound effects on energy

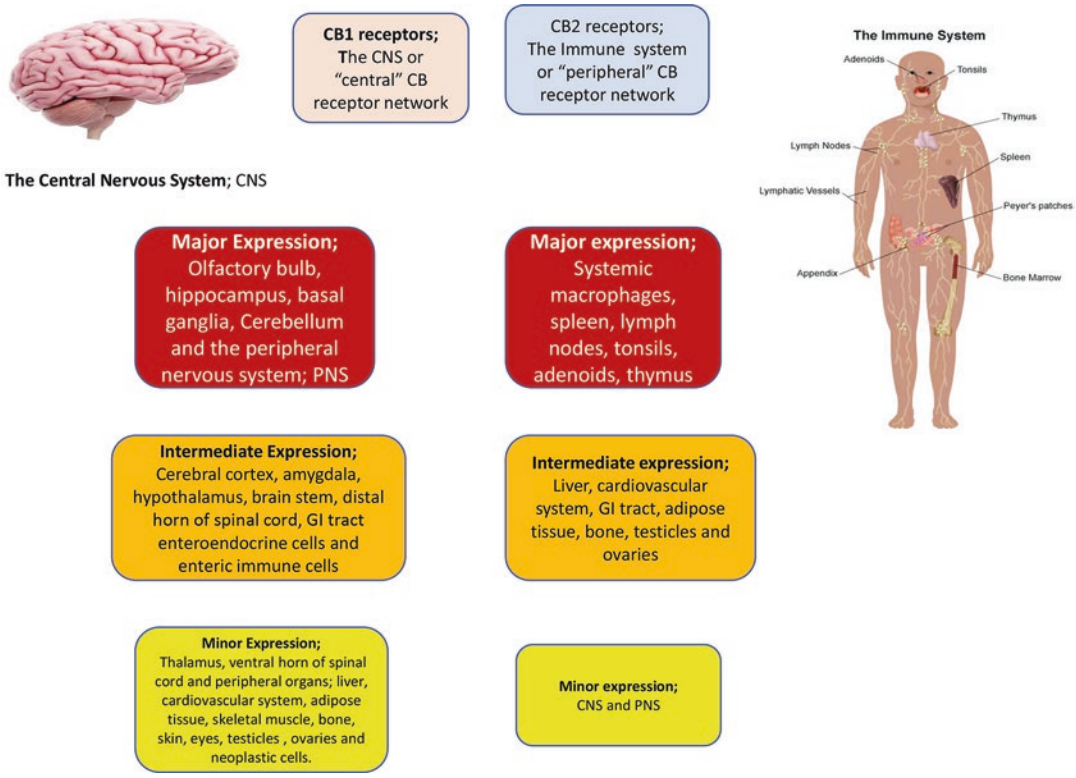

Fig. 12.3 Cannabinoid receptor systemic distribution

balance and caloric intake. One of its major effects is mediated by action on the POMC neurons of the AN via the 5HT 2c receptors. There are thus two distinct sets of POMC neurons: the leptin-responsive subset that increased energy expenditure and the 5HT-responsive subset that is associated with anorexigenic behavior on caloric intake [167, 168]. Further, heterogeneity of POMC neurons based on GABA vs glutamate expression has also been demonstrated.

Dopamine is associated with increased hedonic and reward-associated caloric intake. This is mainly mediated via leptin-sensitive dopamine-producing neurons of the VTA [169]. The dopamine-associated and dopamine-mediated increased food intake appears to be particular for high caloric sweet foods and has been associated with an obese phenotype as well as a trend toward dependency on recreational drugs [170–173]. The dopaminergic neurons from the VTA and the substantial nigra project to the NA, striatum, and the orbitofrontal cerebral cortex and are particularly involved in the hedonic, high-reward caloric intake behaviors that are typical of the so-called "emotional eating."

Nutrient sensing is another important signaling modulator of caloric intake and satiety. Hypoglycemia induces orexigenic feeding responses, while the amino acid L-leucine has anorexigenic effects which are mediated by activation of the mTORC1 pathway in the NPY-/AGRP-producing neurons of the AN as well as the caudiomedial nucleus of the nucleus tractus solitarius (NTS) [174–176]. Fatty acids exert an anorexigenic response via suppression of AMPK in the AN with consequent reduction in NPY production [177].

Figure 12.4 provides an overview of the major elements involved in the hypothalamus' regulatory and modulatory effects on appetite, satiety, and energy balance as well as its interactions with peripheral organs, nutrients, and other parts of the CNS, the PNS, and the autonomic nervous system (ANS) in this regard.

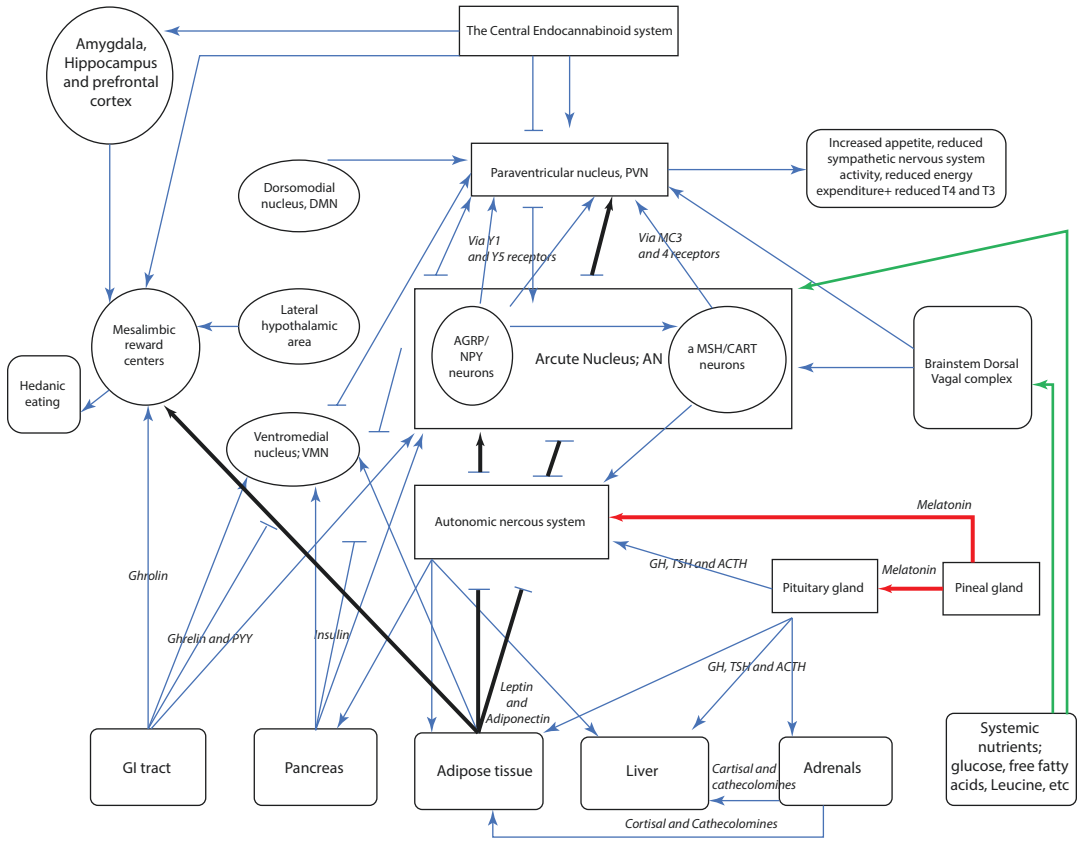

Fig. 12.4 Schematic of the hypothalamic and CNS neurocircuitry modulating satiety, appetite, and energy balance

Hypothalamic Obesity Syndrome (HOS)

Causes of HOS

The causes of HOS are myriad and varied. In some cases, no clear etiologic factor is identified, and so in such cases it is presumed to be idiopathic. Broadly speaking, the known causes of HOS can be categorized into anatomic lesions including post-traumatic, surgical, and irradiation-induced tumors and mass lesions of various sorts, genetic syndromes, and HOS due to the effects of systemically circulating chemicals including various toxins, hormones, and pharmaceuticals/drugs [29, 31–33, 50].

Table 12.3 provides a comprehensive though not exhaustive listing of etiologic considerations in the differential diagnosis of HOS. It is pertinent to note that these etiologies are not mutually exclusive and so in the individual patient afflicted with HOS, multiple etiologies may coexist adding to the complexity of the phenotype and increasing the development of rational, effective management strategies.

More in-depth discussion of the presentation and management of the various mass and structural lesions associated with HOS is provided in other chapters in this textbook.

The etiologic factors listed in Table 12.3 are not exhaustive as more and more CNS disorders and lesions are now being described as being associated with HOS. In cases of HOS seen in the setting of brain lesions like empty sella syndrome, pituitary and/or pineal cysts, Rathke pouch/remnant cysts, hydrocephalus, chronic white matter vascular disease, and other such findings, it is unclear if such findings are the

Table 12.3 Etiologic factors for hypothalamic obesity syndrome

Etiologic factors for hypothalamic obesity syndrome (HOS)
Idiopathic
Empty sella syndrome, hydrocephalus, Froelich's syndrome
Anatomic/structural lesions
Mass lesions: craniopharyngioma, angiosarcoma, cholesteatoma, chordoma, colloid cysts, tumors; endothelioma, ganglioneuroma, ependymoma, epidermoid epithelioma, germinoma, glioma, hamartoma, Langerhans cell histiocytosis (histiocytosis X), leukemia, meningioma, lymphoma, pituitary adenoma (invariably macroadenomas), pinealoma, teratoma, and brain metastases
Inflammatory mass lesions: sarcoidosis, CNS tuberculosis, arachnoiditis, encephalitis
Post-head trauma, post-neurosurgical procedures and surgery, post-cranial irradiation
Cerebral aneurysm
Genetic syndromes, including single gene mutation states and distinctive phenotype-associated genetic syndromes
Congenital leptin deficiency, leptin receptor mutations, single gene mutation states for CART, POMC, prohormone convertase, MC4 receptor, MC3 receptor, brain-derived neurotrophic factor (BDNF), single minded 1 (SIM-1), defective leptin syndrome, Prader-Willi syndrome, Bardet-Biedl syndrome, etc.
Chemicals and pharmaceuticals
Antidepressants, antipsychotics, mood stabilizers, antiepileptics, etc.

cause for the development of the syndrome or "innocent bystanders," and so in many such cases, the HOS is described as idiopathic.

Adiposogenital dystrophy (aka Froelich's syndrome, Babinski-Frohlich's syndrome, Launois-Cleret syndrome, hypothalamic infantilism-obesity syndrome) is an acquired syndrome characterized by tertiary hypogonadism, hyperphagia with often morbid obesity, and associated growth retardation often with onset in childhood. While the syndrome has been described with a long list of structural and anatomic lesions of the hypothalamo-pituitary area including many of the lesions listed in Table 12.3, some cases have been described with no apparent radiologic or anatomic anomaly and are thus described as idiopathic cases. In addition to growth retardation and pubertal-onset delay, the patients with the syndrome may also be associated with chronic headaches, visually derangements, polyuria, and polydipsia. For unclear reasons, it appears to have a male preponderance in prevalence [5, 178–180].

There is no clear topographic correlation between where mass lesions are located and their capacity to induce HOS. Clearly, the reasons for some patients developing HOS from the various listed mass and parenchymal lesions while most patients with these lesions don't develop the syndrome go beyond the location of the mass lesion itself and are likely the result of a confluence of lesion type, location, genetic endowment of the patient, and the resultant local hypothalamic and systemic hormonal milieu.

In some cases, HOS occurs in the setting of an even more uncommon syndrome association: the ROHHAD association which consists of *r*apid-onset *o*besity with *h*ypothalamic dysfunction, *h*ypoventilation, and *a*utonomic *d*ysregulation [181–186]. As a number of the described cases have occurred in the setting of CNS neuroendocrine tumors (NETs), a subset of the syndrome is also described as the ROHHADNET association. While the exact pathogenesis and pathophysiology of the condition remain unclear, there is some evidence to suggest a possible role of autoimmunity in its development [187]. Typically, the syndrome develops in previously healthy and normal young children between ages 2 and 4 years. In ~40–50% of thus far described cases, a NET/neural crest tumor (especially ganglioneuromas or ganglioneuroblastomas) often in the CNS is found. There appear to be less than 100 well-characterized cases of the syndrome published in the medical literature, and it appears it may have been mixed up in the past with congenital central hypoventilation syndrome. The latter is however congenital in origin and thus typically has an earlier age of onset in addition to often being associated with mutations of the PHOX2B *gene* which are absent in ROHHAD which is clearly an acquired syndrome [182, 184, 188–190]. The diagnosis of ROHHAD is a clinical one, and the currently accepted diagnostic criteria were suggested by Ize-Ludlow and colleagues, but the full spectrum of the condition may well change as more cases are identified.

There is also a possibility that some patients may present with wasting as opposed to obesity as was suggested by a case included in the cohort described in the HWS series reported in a young teenage child with metastatic brain gastrointestinal stromal tumor (GIST) [35]. This observation raises the notion that while much more uncommon, cases of wasting may be seen in this syndrome and thus suggest the acronym be further amended to ROWHHAD: *r*apid-onset *o*besity or *w*asting, *h*ypothalamic dysfunction, *h*ypoventilation, and *a*utonomic *d*ysregulation. The ROHHAD syndrome is described in more depth and detail in a separate chapter in this textbook.

The effects of various drugs and other chemicals in inducing HOS appear to be related to the modulatory effects they can have on various neurotransmitters involved in the normal hypothalamic regulation of satiety, appetite, and energy balance. Among the neurotransmitter receptors so affected by antipsychotics, neurolepts, antidepressants, mood stabilizers, antiepileptics, etc., are GABA, dopamine, serotonin, histamine, cannabinoid, muscarinic, and glutamate receptors [166, 191–195]. Among the most extreme offenders in this regard are clozapine and olanzapine. It is important to appreciate that as regards the effects of various neuroactive medications and pharmaceuticals on weight and other aspects of hypothalamic function, there is considerable heterogeneity. The effects of these agents in the individual patient are modulated by a host of patient intrinsic and extrinsic factors including innate genetic endowment, the presence of familial obesity, diet and other lifestyle activities, duration and dosage used, and the milieu of other concomitant medications. The selective serotonin reuptake inhibitors (SSRIs) illustrate this very aptly with variable effects ranging from profound weight gain to weight loss described for the same SSRIs in different patients based on variables such as duration of use and innate genetics [196–199]. Table 12.4 details the major neuroactive medications and pharmaceuticals associated with the development of the HOS phenotype in select patients. Weight gain post-CNS surgery in the hypothalamo-pituitary area is the most common etiologic factor identified in HOS, and estimates

Table 12.4 Neuroactive medications and pharmaceuticals associated with the development of the HOS phenotype

CNS and hypothalamic acting medications and pharmaceuticals associated with HOS phenotype
Antidepressants: monoamine oxidase inhibitors, tricyclic antidepressants including nortriptyline, amitriptyline, doxepin, imipramine, clomipramine, trimipramine, desipramine, etc.
Selective serotonin reuptake inhibitors (SSRIs) including paroxetine, citalopram, escitalopram, sertraline, fluoxetine, mirtazapine, etc.
Others: maprotiline, isocarboxazid
Antipsychotics: thioridazine, quetiapine, clozapine, risperidone, chlorpromazine, perphenazine, trifluoperazine, zotepine, sulpiride, chlorpentixol, asenapine, iloperidone, paliperidone, risperidone, sertindole, olanzapine, etc.
Antiepileptics: valproate, phenobarbital, divalproex, etc.
Mood stabilizers: lithium, carbamazepine, valproate, gabapentin, etc.

suggest that approximately a third of patients undergoing such surgical procedures developed significant weight gain post-procedure with other clinical features consistent with HOS [33]. The most common of this post-surgical HOS is following craniopharyngiomas, and patients with more extensive hypothalamic destructive damage evidenced by imaging findings tended to have more postoperative weight gain [25, 29, 200].

The Bardet-Biedl (aka Laurence-Moon-Biedl) syndrome which is discussed further below is one of several genetic syndromes associated with HOS. It is primarily characterized by retinal rod/cone dystrophy, polydactyly, mental retardation, renal dysfunction, and hypogonadotropic hypogonadism. Over 50% of patients with this syndrome have associated obesity with ~15% having accompanying morbid obesity [33, 201].

A greater appreciation of the heterogeneity of HOS and the associated clinical, biochemical, and neurohumoral changes associated with it as well as the various potential causes and contributors to its onset has led to an increasing realization that while certainly not as common as "idiopathic obesity," it is significantly not as rare as previously presumed. Better understanding of the pathophysiology and pathogenesis of HOS has also led to a better understanding of the regulation of energy balance, satiety, and appetite as

well as a better understanding of important determinants and predictors for the development of idiopathic obesity as well as hypothalamic dysfunction syndromes (HDS) [29–33, 35, 50].

Genetic Syndromes of HOS

Genetic endowment and the phenotypic expression thereof play a vital role in the etiology and expression of the HOS. While a full detailing and description of the various genetic syndromes of hypothalamic disease states is the subject of another chapter in this textbook, this section gives brief descriptions and listings of the most common and well-characterized genetic conditions identified to be associated with HOS. These can be broadly categorized into monogenic obesity syndromes, distinctive polysomatic syndromes with HOS as part of the phenotypic complex, and otherwise "idiopathic" HOS states associated with polygenic *gene* profiles already known to be associated with common obesity but also described in unique patients to predispose to the development of a HOS phenotype.

The powerful instrument of genome-wide association scans (GWAS) and the availability of numerous large well-characterized study patient cohorts worldwide with excellent phenotyping and available stored DNA samples have enabled the compilation of a fairly comprehensive and still growing list of various *genes* with demonstrated hypothalamic expression and relationship to obesity development. The clinical effect size of most of these *gene* SNPs on the development of HOS is relatively small, but the possibility of additive effects in patients with multiple SNPs does make their recognition and cataloging important in complete genotyping of individual patients to develop more precision medicine targeted medication and other intervention strategies [202].

Included in this list are the following *genes*: phosphofructokinase platelet *gene* (PFKP), fat mass and obesity-associated *gene* (FTO) transmembrane protein 18 (TMEM 18), melanocortin 4 receptor (MC4-R), leucine zipper transcription regulator 2 (SEC16B), solute carrier family39 (zinc transporter) member 8 (SLC39A8), brain-derived neurotrophic factor (BDNF), glucosamine-6 phosphate deaminase 2 (GNPDA2), G protein-coupled receptor family C group 5 (GPRC58), IQ motif containing K (IQCK), protein kinase D1 (PRKD1), SH2B adaptor protein 2 isoform 1(SH2B1), apolipoprotein B48 receptor (APOB48R), sulfotransferase family cytosolic (SULT1A2), ataxin2-related protein (ATXN2L), Tu translation elongation factor, mitochondrial (TUFM), gastric inhibitory polypeptide receptor (GIPR), glutaminyl-peptide cyclotransferase-like (QPCTL), ets variant *gene* 5 (ETV5), POMC, Dnaj (heat shock protein 40) homologue subfamily C member 27 (DNAJC27), adenylate cyclase 3 (ADCY3), neuronal growth factor 1 (NEGR1), transcription factor AP-2 beta (TFAP2B), mitogen-activated protein kinase 5 (MAP 2K5), SK family transcriptional corepressor 1 (SKOR1), neurexin 3 (NRXN3), Fas apoptotic inhibitory molecule (FAIM), catenin beta-like 1 (CTNNBL1), leucine-rich repeat and Ig domain (LRRN6C), 3-hydroxy-3-methyglutaryl coenzyme alpha reductase (HMGCR), POC5 centriolar protein (POC5), Fanconi anemia complementation group L (FANCL), immunoglobulin superfamily member 4D (CADM2), transmembrane protein 160 (TMEM160), zinc finger CCH-type containing 4 (ZC3H4), low-density lipoprotein-related protein 1B (LRP1B), mitochondrial translational initiation factor 3 (MTIF3), transcription factor 3A (GTF3A), prolactin (PRL), TNNI3 interacting kinase (TNNI3K), zinc finger protein 608 (ZNF608), mitochondrial carrier 2 (MTCH2), NADH dehydrogenase (ubiquinone) fe-s protein 3, NDUFS3, CUG triplet repeat RNA-binding protein 1 (CUGBP1), potassium channel tetramerization domain (KCTD15), polypyrimidine tract binding protein 2 (PTBP2), tubby *gene* (TUB), ribosomal protein L27a (RPL27A), nudix-type motif 3 (NUDT3), high-mobility group AT-hook 1 (HMGA1), Niemann-Pick disease type C1 precursor (NPC1), v-maf musculoaponeurotic fibrosarcoma oncogene (MAF), and phosphotriesterase related (PTER) [202].

Monogenic HOS

These conditions as a group are generally autosomal recessive linked, and while heterozygous carriers of the at-risk mutations are generally phenotypically normal, the homozygous patients have a high degree of obesity phenotypic penetrance that is often very early in onset, often associated with morbid obesity and a nearly 100% obesity phenotype expression [202].

Leptin *Gene* Mutations

First described by Friedman and colleagues in 1994, the discovery of leptin and subsequent elucidation of its central role in energy balance, satiety, and appetite regulation in vertebrates and humans provided a quantum leap to our understanding of the central neurocircuitry involved in centrally mediated obesity and wasting syndromes [23]. The subsequent description of mouse models and then human patients with leptin deficiency and the amelioration of the clinical phenotype with leptin replacement begin the earnest the era of molecular therapeutics for unique forms of genetically determined obesity [203–205]. A more in-depth description of the leptin-deficient phenotype will be provided in the chapter on genetic disorders of hypothalamic function, but for this discussion it is important to note that though a rare form of obesity, its recognition is vital because of the huge potential for therapeutic benefit in this group of patients from leptin replacement. It is characterized by early-onset childhood obesity with marked hyperphagia, unrelenting hunger, and subsequent rapid-onset obesity which is invariably of morbid degree by the time the patient comes to medical attention. The syndrome is also often associated with hypogonadotropic hypogonadism [203, 206–214]. In view of its autosomal recessive mode of inheritance, it is not surprising that leptin deficiency mutations in humans are often associated with consanguineous families [215, 216]. Despite the initial great hoopla regarding the potential of leptin as a therapeutic agent from more common idiopathic so-called "common" obesity, however, this form of obesity unlike leptin-deficient obesity is typically associated with hyperleptinemia and associated leptin resistance with little therapeutic response to pharmacologic dose leptin administration. In addition, while leptin deficiency has a well-defined phenotype in humans and animals associated with features of the HOS, hyperleptinemia typically does not cause the converse and is not typically associated with significant hypophagia, hypermetabolism, nor wasting syndromes. It is however also important to be aware of an even more rare form of leptin deficiency associated with the production of a biologically inert leptin which is however measured by available serum assays resulting in the unique scenario of a leptin-deficient clinical phenotype of severe early-onset obesity, HOS, but measurable hyperleptinemia and distinct from "common" obesity associated with marked clinical response to biologically active leptin replacement therapy [217].

Leptin Receptor Mutations

This clinical syndrome is like leptin deficiency associated with established animal models (including the Db/Db mouse and the fatty Zucker rats) as well as human patients. Though phenotypically resembling leptin deficiency, the underlying pathophysiology is distinct and different [203]. Unlike leptin-deficient patients and animals, this is associated with hyperleptinemia and poor response to attempts at leptin replacement therapy. Similar to leptin-deficient animals and humans, the syndrome is characterized by early-onset rapidly progressive morbid obesity with hyperphagia and lack of satiety, hypogonadotropic hypogonadism, but distinct from leptin-deficient patients also with adenohypophyseal dysfunction including reduced IGF-1 and growth hormone secretion with potential for development of clinically significant growth hormone deficiency. In addition, these patients may also have tertiary hypothyroidism but tend to have normoglycemia with normal insulin profiles and insulin sensitivity as well as normal lipid profiles despite their profound obesity.

BDNF Mutations This clinical phenotype as with most of the monogenic forms of obesity is rare and phenotypically can result from

mutations of BDNF or of its receptor, the tyrosine kinase receptor tropomyosin-related kinase b (TRKB). They are both involved in normal MC4-R signaling [218]. This syndrome is again associated with early-onset morbid obesity in children associated with hyperphagia in addition to impaired short-term memory, hyperactivity, learning disabilities, and/or mental retardation. It is very rare and associated with a corresponding mouse model [219–222].

MC4 Receptor Mutations (MC4-R) MC4-R mutations are the most common form of monogenic obesity in humans. There are also well-characterized mouse models of this condition [70]. While there is a suggestion that these mutations occur in ~0.5% of the general population, among morbidly obese adolescent and children, the prevalence of this *gene* mutation has been suggested to be as high as 2–6% [202, 223–229]. Over 160 distinctive functionally important mutations of the MC4-R *gene* are now known, and while less prevalent among cohorts of adult-onset obesity (1–2%), its recognition and identification in human obesity workup are very important as it influences treatment strategies and the response to planned interventions including pharmacotherapy and elective bariatric surgery [69, 230–235]. In vitro studies have demonstrated that most MC4-R mutations result in loss of function states and consequently impairment of the normal satiating effect of α-MSH in the hypothalamus [231, 236, 237]. Based on this, it is not surprising that the clinical phenotype of this syndrome is characterized by hyperphagia and higher threshold for satiety. In addition, energy expenditure is reduced as well as other distinctive phenotypic expressions including growth acceleration, hyperinsulinemia, normal leptin levels, and increased bone density [238, 239]. The association between MC4-R mutations and binge eating disorder is not fully elucidated and currently is the subject of some controversy [240–243]. It is estimated that the presence of MC4-R mutations/functional impairing polymorphisms can account for ~4.5–9.5 kg/m^2 incremental BMI increase in MC4-R mutations. Homozygous as well as those with compound heterozygous carriers typically have a morbidly obese phenotype, and it is now apparent that MC4-R mutations beyond association with monogenic obesity syndromes can also be implicated and involved in the development of polygenic obesity states that can be associated with HOS. Individuals with simple heterozygous mutations have a less severe clinical phenotype. Overall though, the effect of MC4-R mutations on the clinical obesity phenotype is generally not as marked as that associated of leptin and leptin receptor *gene* mutations [223, 239, 244, 245].

Another very rare and distinctive monogenic obesity syndrome is that due to mutations of the melanocortin 2 receptor accessory protein 2 (MRAP2) *gene*. It is characterized by early-onset childhood obesity with nondistinctive phenotypic, dysmorphic, or syndromic identifiers and is associated with marked hyperphagia with deranged/absent satiety [246–248].

CART *Gene* Mutations

These are very rare and characterized by defective modulation of leptin on CART expression in the hypothalamus as well as defective leptin-mediated ARC peptide expression in the sympathetic nervous system. The mutations identified are generally heterozygous missense mutations associated with either childhood- or adult-onset obesity phenotypes associated with reduced metabolic rate but with normal serum circulating leptin levels [99, 249].

POMC Mutations

POMC is the neurochemical precursor of α-MSH which is a central effector of leptin's anorexic and satiety-inducing effects in the hypothalamus that is mediated via the MC4-R and MC3-Rs. POMC mutations are another rare monogenic obesity syndrome, and the vast majority of patients with the typical associated syndrome have homozygous or compound heterozygous mutations [247, 250, 251]. The clinical syndrome is characterized by early-onset childhood obesity associated with significant hyperphagia, blunted satiety, and secondary adrenal insufficiency which can present during the neonatal period

with vascular collapse and adrenal crises. This is due to POMC also being the precursor molecule for ACTH production, thus resulting in ACTH deficiency in these patients. Again because of POMC being the precursor molecule for the spectrum of MSHs which are involved in normal pigmentation development, patients with this syndrome often also have distinctive pigmentary changes including distinctive red hair, striking pallor, and extensive freckling [72, 252–254]. There have been some recent clinical trials exploring the potential utility of designer selective melanocortin receptor antagonists including setmelanotide with some limited success [252, 255–261].

Prohormone Convertase 1 *Gene* Mutations

This is another rare form of genetic obesity of monogenic origin and is characterized by defective or deficient expression of the proprotein convertase/subtilisin/kexin type 1 *gene*. This results in deficiency of the proprotein convertase 1/3 resulting in multihormonal deficits since this enzyme is critical to the normal splicing of POMC to liberate ACTH and α-MSH. It is again characterized by early-onset morbid childhood obesity with secondary adrenal insufficiency due to ACTH deficiency, impaired glucose tolerance with postprandial hypoglycemia, hypogonadotropic hypogonadism, elevated serum levels of both POMC and proinsulin, and reduced serum insulin levels. In addition, these patients tend to have elevated progastrin and proglucagon levels with normal serum leptin despite their marked obesity [71, 262]. There have also been identified SNPs of the *gene* seen clinically to be associated with the obesity phenotype in Caucasians but not Asians for reasons that remain unclear [263].

Tubby *Gene* Mutations

Tub *gene* mutations and rare monogenic form of obesity have only recently been recognized. While there is a murine model of the syndrome, the pathophysiologic basis of the syndrome is not fully elucidated at this point. What is known is that the *gene* product is a peptide expressed in adipose tissue and various hypothalamic nuclei and that the syndrome in mice and humans is the result of loss of function mutations of the TUB *gene*. It appears that the *gene* product is involved in normal AGRP expression and function in the hypothalamic AN. The clinical syndrome in humans is characterized by early-onset childhood morbid obesity with retinal dystrophy associated with night blindness (nyctalopia). A history of familial consanguinity has been identified in affected human cohorts, and it has thus far only been described in Caucasian patients [264–269].

The spectrum of monogenic causes of obesity is likely to continue to grow as genetic interrogation and GWAS studies continue to be applied to unique individual patients and previously unstudied population groups and cohorts. Among the emerging other monogenic obesity syndromes are mutations of the SRC homology 2B adapter protein 1 (SH2B1) *gene* [270, 271]. The *gene* product modulates signaling by myriad chemical mediators and hormones that act via tyrosine kinase or JAK-associated cytokine receptors including leptin, insulin, growth hormone, and nerve growth factor. A knockout mouse model of this monogenic obesity exists and is characterized by hyperphagia obesity and insulin resistance. Humans with loss of function mutations of the *gene* have been identified in large cohort screenings, and the syndrome in humans is characterized by early-onset severe childhood obesity with hyperphagia, marked insulin resistance, and reduced linear growth with reduced adult final height. Additionally, these patients have a wide spectrum of associated behavioral anomalies including (but not restricted to) social isolation and hyperaggression.

Another recently emerging monogenic obesity syndrome is that due to mutations of the single-minded 1 (SIM1) *gene* [272]. The affected patients here are hyperphagic with autonomic dysfunction in addition to early-onset often morbid obesity. Carriers of SIM1 mutations have in addition been associated with speech and language delays and other neurobehavioral defects including autistic features. The clinical syndrome associated with SIM1 is oft described as Prader-Willi-"like" because of similarities observed in

the clinical presentation of these patients to those with the established Prader-Willi syndrome. The SIM1 *gene* product is a transcription factor required for normal development of the supraoptic nucleus and PVN. Consequently, it is not surprising that some patients with this mutation have associated reduced hypothalamic oxytocin production. They also tend to have accelerated liner growth, hyperleptinemia, and hyperinsulinemia [273–275].

Syndromic HOS

These forms of HOS are characterized by distinct clinical phenotypes with varying degrees of manifestation of the HDS, dysmorphia, and organ-specific developmental features. They are typically associated with early childhood onset, and the identified cause is either idiopathic or known but not typically due to distinct single *gene* mutations [276, 277]. There are over 25 distinct forms of syndromic obesity, and their clinical presentation is quite heterogenous, while the vast majority of those presently described and recognized are quite rare. The following description provides some detail only on the most common forms of these associated with HOS clinical presentation. In some cases, these syndromes are associated with pleiotropy wherein a single *gene* mutation may be associated with multiple seemingly unrelated and unconnected clinical manifestations in patients with the syndrome [278, 279]. Contiguous *gene* syndrome is another phenomenon sometimes seen in syndromic HOS and is characterized by deletion of a contiguous set of *genes* presenting with a multivariate clinical syndrome where each of the deleted *genes* is responsible for one or more of the unrelated clinical features of the complete clinical syndrome. Segmental aneuploidy is a special form of contiguous *gene* syndrome that is epitomized by the Prader-Willi syndrome (PWS). Table 12.5 provides a broad summary of the best defined syndromic entities associated with HOS, most of which are very rare. We will provide brief descriptions of the most common of these entities.

The Prader-Willi Syndrome (PWS)

PWS is the most common form of HOS with an estimated prevalence of ~1 in 10,000–30,000 live births. The major presenting features are neonatal hypotonia, initial feeding difficulties, and inadequacy in the neonatal and early infancy period, then followed by progressive hyperphagia, voracious appetite and early-onset excess weight gain, obesity development (often morbid in degree) along with hypogonadism (invariably hypogonadotropic), and mental handicap with mean IQ of ~65 [13, 278, 280–282]. While primary amenorrhea is common in girls with PWS, it is not universal (~56% of cases) as spontaneous onset of menarche and subsequent irregular menses with fertility potential are described in other female patients (~44% of cases) [283]. Examination findings include almond-shaped eyes, thin upper lips, downturned corners of the mouth bilaterally, narrow face, and behavioral features like skin picking, stubbornness, and temper fits. Variable sleep anomalies, small hands and feet, and short stature are other described features. Cryptorchidism is particularly common among young boys with PWS. Children with PWS often also have growth hormone secretory deficits and reduced IGF-1 secretion. In addition, they tend to have fasting and postprandial ghrelin elevation, hyperleptinemia, and essentially normal insulin dynamics despite the associated obesity. Patients with PWS have also been described to have small PVNs with paucity of oxytocin neurons. Holm and colleagues developed a clinical scoring system to assist with clinical diagnosis of the condition based on identified major, minor, and supportive criteria. A score of 5 points, of which 4 need to be major criteria, is usually required for diagnosis in children under 3 years, while the point threshold is 8 (of which 5 need to be major points) for patients 3 years or older [284]. PWS is associated with uniparental disomy and caused by absent expression of the paternal-derived *genes*, small nuclear ring finger (SNURF), small nuclear ribonucleoprotein polypeptide N (SNRPN), makorin ring finger protein 3 (MKRN3), MAGE family member 2 (MAGE2), and Necdin MAGE family member (NDN) *genes* all from the imprinting region

Table 12.5 Clinical spectrum of disorders associated with syndromic HOS

Summary of the spectrum of syndromic forms of HOS					
	Syndrome	Estimated prevalence	Inheritance pattern	Affected gene(s)/chromosomal region(s)	Distinctive clinical features
1	Prader-Willi syndrome	1 in 10–30,000	Familial and sporadic	15Q 11.2-Q13 paternal-derived loss	Morbid obesity, hypothyroidism, hair hypopigmentation, hip dysplasia, sleep apnea, scoliosis
2	Prader-Willi-"like" syndrome	Very rare	Familial and sporadic	1P36.3, 2P21, 3P26.3, 6Q, 9 Q34, 10Q26, 12 Q maternal-derived loss	Prader-Willi-like phenotype + cardiac defects, seizures, and hearing deficits
3	Bardet-Biedl syndrome	1 in 13–160,000	Autosomal recessive	BBS1-20, NPHP1, FBN3 + CEP19 mutations	Cognitive deficits, visual deficits, hypogonadism, anosmia/hyposmia, speech deficits + ataxia
4	Alstom's syndrome	1–9 in 1,000,000	Autosomal recessive	ALMS1 mutations	Visual defects, sensorineural hearing deficits, male hypogonadism, female hyperandrogenism, short stature, restrictive cardiomyopathy
5	Carpenter's syndrome	<1 in 1,000,000	Autosomal recessive	RAB23 + MEGF8 mutations	Craniofacial dysmorphia, syndactyly. Other skeletal, dental anomalies
6	Borjeson-Forssman-Lehmann syndrome	<1 in 1,000,000	X-linked recessive	PHF6 mutations	Mental retardation, hypogonadism, short stature
7	Choroideremia-deafness obesity/Ayazi syndrome	<1 in 1,000,000	X-linked recessive	Xq21 deletions including CHM + POU3F4 genes	Visual anomalies, mental retardation, sensorineural + conductive deafness
8	Cohen's syndrome	Very rare	Autosomal recessive	VPS13B deletions or mutations	Facial dysmorphia, microcephaly, hypotonia + happy disposition.
9	Coffin-Lowry's syndrome	1 in 50–100,000	X-linked dominant and sporadic	RPS6KA3 mutations	Growth + psychomotor retardation, microcephaly, seizure disorder
10	CHOPS; *c*ognitive deficit + *c*oarse facies, *h*eart defects, *o*besity, *p*ulmonary dysfunction, *s*hort stature syndrome	Very rare	Autosomal dominant	AFF4 mutations	As per syndrome acronym
11	16P11.2 microdeletion syndrome	Very rare	Autosomal dominant	16P11.2 (SH2B1) deletion	Morbid obesity, developmental delay, neuropsychiatric syndromes
12	Coloboma, microphthalmia, obesity, hypogonadism, mental retardation syndrome	<1 in 1,000,000	Autosomal dominant	Unknown	As per syndrome description
13	Fragile X syndrome	1 in 4–5000	X-linked dominant	FMR1 mutations	Mental retardation, facial dysmorphia, ADHD phenotypes, morbid obesity, macroorchidism

14	Hydrocephalus, obesity, hypogonadism/ Sengers-Hamel-Otten syndrome	Very rare	X-linked recessive	Unknown	Congenital hydrocephalus, mental retardation, hypogonadism, and short stature
15	Facial dysmorphia obesity, brain malformation, mental retardation syndrome	<1 in 1,000,000	Autosomal recessive	TRAPPC9 mutations	Hypotonia, microcephaly, and seizure disorder
16	Prognathia, eye + skin anomalies, obesity mental retardation/MOMES syndrome	<1 in 1,000,000	Autosomal recessive	4q35.1 deletion + 5P14.3 duplication	Macrocephaly
17	Seizure, macrocephaly, obesity mental retardation syndrome	<1 in 1,000,000	unknown	Der 8;12 translocation P23.1-13.31 deletion	Developmental delay, dysmorphia, unsteady gait, dental/palate anomalies
18	X-linked microcephaly, seizures, hypogonadism, obesity, mental retardation/MEHMO syndrome	<1 in 1,000,000	X-linked recessive	EIF2S3 mutations	As per syndrome description
19	Microcephaly osteodysplasia primordial dwarfism; MOPD type 2/Majewski type 2 syndrome	Very rare	Autosomal recessive	PCNT mutations	Marked short stature, mental retardation, café au lait spots
20	Macrocephaly obesity mental retardation ocular anomaly/MOMO syndrome	<1 in 1,000,000	Autosomal dominant	Chr 16; 20 Q21; P11.2 reciprocal translocation	Obesity with and overgrowth, behavioral anomalies
21	Mental retardation obesity retinal dystrophy micropenis/MORM syndrome	Very rare	Autosomal recessive	INPP5E mutations	As per syndrome description
22	Wilms' tumor, aniridia, renal malformation, mental retardation/WAGR syndrome	~1 in 1,000,000	Autosomal dominant	Deletions in 11P13-14.1; WT1, PAX6, BDNF	Behavioral anomalies with autism-like features, cryptorchidism
23	Rubinstein-Taybi/broad thumb-hallux syndrome	~1 in 100,000–125,000	Autosomal dominant and sporadic	CREBBP +/− EP300 mutations or deletions	Microcephaly, cryptorchidism, behavioral problems, orthopedic problems
24	Pseudohypoparathyroidism + Albright's hereditary osteodystrophy syndrome	Very rare	Autosomal dominant	GNAS mutations or duplications	Short stature, resistance to PTH, TSH, GHRH + gonadotropins, hypogonadism, osteoporosis
25	Diploid triploid mosaicism syndrome	Very rare	Mosaicism	Unknown	Short stature, learning disabilities, seizure disorder, hearing loss
26	Dwarfism brachydactyly obesity global developmental delay syndrome	<1 in 1,000,000	Autosomal recessive	PRMT7 mutations	As per syndrome description
27	X-linked mental retardation gynecomastia obesity/Wilson-Turner syndrome	Very rare	X-linked recessive	LAS1L and HDACB mutations	Hypogonadism, short stature, speech impediments, emotional lability
28	Single-minded 1 (SIM1) hyperphagia-obesity syndrome	Very rare	Unknown	SIM1 (6q16.2) deletions/ haploinsufficiency	Early-onset morbid obesity, small PVNs, reduced hypothalamic oxytocin, hyperleptinemic + hyperinsulinemic

15Q11.2-q13 [278]. While paternal-derived *gene* deletion is the most common cause of PWS (70–75% of cases), there have also been descriptions of the syndrome due to maternal-derived uniparental disomy (20–25% of cases) or imprinting defects of the critical region (1–3% of cases). Methylation-specific multiplex ligation-dependent probe amplification analysis (MS-MLPA) is the gold standard methodology for diagnosis of PWS, but further testing such as fluorescence in situ hybridization (FISH) or chromosomal microarrays is required to define the specific genetic subtype. This methodology is also able to distinguish PWS from the Angelman syndrome (aka the happy puppet syndrome) which is genetically related to PWS but phenotypically distinct and in contrast may be associated with HWS and is described further in that section of this chapter. Among important differential diagnostic considerations for PWS in infancy when the phenotype is particularly heterogenous include Angelman syndrome, fragile X syndrome, Bardet-Biedl syndrome, Cohen syndrome, Borjeson-Forssman-Lehmann syndrome, Prader-Willi-"like" syndromes, Alstrom's syndrome, and 16P11.2 microdeletion syndromes [278].

Prader-Willi-Like Syndromes (PWLS)

This is a heterogenous clinical entity characterized by patients with phenotypic features akin to PWS but without the typical chromosomal disruptions/deletions on the chromosome 15Q region. In addition, these patients tend to have additional phenotypic features not typical of PWS including cardiovascular defects and neurologic deficits including seizure disorders and/or hearing loss [273, 274, 285]. PWLS is both clinically and genetically heterogenous. The phenotype has been described in association with copy number variations on several chromosomal locations including 1P36.3, 2P12, 3P26.3, 6Q, 9P34, 10Q26, 12 Q, and chromosome X. It has also been described in association with uniparental disomy on chromosome 14. In patients with suspected PWLS, chromosomal microarrays are the diagnostic test of choice to establish a genetic/chromosomal diagnosis for the clinical phenotype in the individual patient. One importantly distinct form of PWLS is those with chromosome 6Q deletions which are associated with loss of the single-minded (SIM1) *gene* which is involved in the leptin melanocortin signaling pathway.

Bardet-Biedl (Laurence-Moon-Biedl) Syndrome

Bardet-Biedl syndrome is a ciliopathy with estimated prevalence ranging from ~1 in 13,500 patients in Israel and Arabian countries to ~1 in 160,000 in Swiss patients. Consanguinity appears to be the main cause of the wide variance in prevalence between these two populations [286, 287]. It is characterized by a cone-rod retinal dystrophy, polydactyly, cognitive deficits including marked mental retardation, hypogenitalism, cryptorchidism, and hypogonadism in older subjects as well as renal anomalies. Also seen in the clinical phenotype are speech impediments, anosmia or hyposmia, psychiatric syndromes, ataxia, and type 2 diabetes [288–290]. Many of the distinctive clinical features are not present at birth nor during infancy. The ophthalmic features in particular are late in developing with nyctalopia typically developing at ~ age 7–8 years with near total legal blindness often present by age 20 years old in >60% of patients. The diagnosis is clinical and based on the presence of a least four major diagnostic features. When there are only three such criteria, the presence of at least two minor criteria is also diagnostic. Important differential diagnoses to consider when Bardet-Biedl is being considered are other ciliopathies such as Alstrom's syndrome and the McKusick-Kaufman syndrome. From a molecular diagnostic perspective, Bardet-Biedl is a very heterogenous condition with over 23 distinct *genes* thus far identified to be associated with its development. These include BBS1-20, nephrocystin 1, fibrillin 3, and centrosomal protein 19 [288–290]. Most (~20–23%) of the cases of the syndrome in European and North American populations are due to mutations in the BBS 1 and 10 *genes*. The inheritance of Bardet-Biedl is com-

plex and variable with autosomal recessive, sporadic, and triallelic inheritance patterns described. Next-generation sequencing panels offer the most efficient means to establishing exact molecular diagnoses in a timely fashion. While there is no clear genotype to phenotype correlation in Bardet-Biedl, it does appear that patients with BBS1 mutations tend to have a less clinically disruptive phenotype compared to other *gene* mutations.

Wilms' Tumor, Aniridia, Genitourinary Malformations + Mental Retardation (WAGR) Syndrome

WAGR syndrome was first described by Miller and colleagues in 1964 as an autosomal dominant linked syndrome with an estimated prevalence of ~1 in 1,000,000 patients [291–293]. Obesity, somatic overgrowth, and hyperphagia have been described in a subset of these patients and are sometimes then referred to by the acronym WAGRO [294–297]. Some cases have been associated with hemihypertrophy, and when the full clinical spectrum of features is present, it is a distinctive syndrome that is pathognomonic with very few viable significant differential diagnostic considerations.

WAGR is typically caused by a deletion of the 11P13 chromosomal section and consequently results in total loss or haploinsufficiency of the Wilms tumor (WT1) and paired box 6 (PAX6) *genes*. These two *genes* appear to be the major mediators of the clinical phenotype with WT1 being tumor suppressor *gene* whose loss results in increased risk of Wilms tumor development, while PAX6 (its *gene* product is a transcription factor) insufficiency results in ocular, brain, and pancreatic defects. Some cases of WAGR also implicate the brain-derived neurotrophic factor (BDNF *gene*), and this is suggested to be the major mediator of the obesity associated with the syndrome. All cases of WAGR involving BNDF disruption are associated with the obesity phenotype in contrast to ~20% with obesity in WAGR patients with normal BDNF expression. BDNF's *gene* product is a member of the nerve growth factor family of peptides important for the development, proliferation, and survival of distinctive neuronal cell populations. It appears that BDNF acts in the VMH as a terminal target of the MC4-R, hence its role in modulation of satiety and energy balance. Genetic testing in children with appropriate clinical phenotypes is typically done using high-resolution cytogenetics. If these show no anomalies, however, then the possibility of smaller deletions then needs to be considered in which case FISH, methyl-specific multiplex ligation-dependent probe amplification analysis, and/or array comparative genome hybridization may then need to be done.

Somewhat related to but distinct from WAGR is the Beckwith-Wiedemann syndrome (BWS) that is the result of a plurality of possible chromosomal and genetic mutations in the region of 11P15.5 which is topographically close to that associated with WAGR. BWS is known to be associated with an increased risk for the development of Wilms tumor [298–303]. It is associated with imprinting dysregulation of several *genes* in that chromosomal region including the IGF-2 *gene* and is not unexpectedly thus associated with hyperinsulinemia, hypoglycemia, and intolerance of fasting. Hemihypertrophy and other forms of generalized somatic overgrowth are also a common phenotypic feature of the syndrome; however, some cases have been described associated with morbid obesity of early onset especially in children. It has been demonstrated that loss of imprinting and/or loss of function mutations or haploinsufficiency impacting the IGF2 *gene* and/or the imprinted center region 1 (ICR1) *gene* can result in the two disparate clinical phenotypes of BWS and Russell-Silver syndrome akin to the variable phenotypes associated with PWS and Angelman syndrome.

Alstom's Syndrome

Alstrom's syndrome first described by Alstrom and colleagues in 1959 is another ciliopathy. Its estimated prevalence is 1–9 patients per 1,000,000 with less than 1000 well-described and detailed cases in the reported medical literature [304–306].

It is a heterogenous disorder characterized by obesity, cone and rod retinal dystrophy with consequent visual deficits, renal anomalies, male hypogonadism, female hyperandrogenism, and short stature in adulthood. Bardet-Biedl syndrome is an important differential diagnostic consideration. Other associated features of Alstrom's syndrome are progressive sensorineural deafness, type 2 diabetes, and dilated or restrictive cardiomyopathy. While visual problems commence in Alstrom's syndrome in early childhood (generally at under 2 years of age), its onset occurs later in Bardet-Biedl syndrome. In addition, unlike Bardet-Biedl syndrome, polydactyly is not associated with Alstrom's syndrome. Definitive distinction between the two syndromes is however most reliably achieved by obtaining genetic and molecular analyses.

The syndrome is the result of homozygous or compound heterozygous mutations of Alstrom's syndrome protein 1 (ALMS1) on chromosome 2p 13. There are also a few described cases of the Alstrom's syndrome found to be the result of triallelic *gene* mutations especially among patients of Turkish descent. ALMS1 is involved in microtubule organization, ciliary transport, endosome recycling, and cell cycle regulation. Type 2 diabetes risk in Alstrom's syndrome is greater than in Bardet-Biedl even with comparable BMIs. The exact function and role of the ALMS1 *gene* product on energy balance, appetite, and satiety is not fully understood at this point. The molecular diagnosis is confirmed using mutation analysis of potential *gene* mutation hot spots on target exons of the *gene*. Microarray scanning and whole exome and genome sequencing are more comprehensive methods being used more widely both for confirmation of the diagnosis and for excluding potential differential diagnoses.

16P11.2 Microdeletion Syndrome

This is again a heterogenous group of disorders often characterized by autism spectrum disorders, schizophrenia, and/or other neuropsychiatric disease states. This syndrome is estimated to occur in ~1% of population-based autism spectrum disorders [307–309]. The syndrome is also typically characterized by morbid early-onset obesity, global developmental delay, and mental retardation with hypotonia, seizure disorder, behavioral problems, and a high prevalence of speech anomalies. Microduplications as opposed to deletions of this chromosomal zone have been described and are associated with a wasting syndrome along with other features common to the microdeletion syndrome and thus typical of the HWS [310, 311]. The exact genetic basis for the syndrome manifestations remains unclear. The typical deleted region is ~593 kb in size, but larger deletions in this chromosomal zone of ~1.7 mb including the typical 593 kb microdeletion region are associated with the same clinical phenotype as detailed above in addition to other features like facial dysmorphia, cardiac defects, and/or aganglionic megacolon (Hirschsprung's disease) [312–317]. PWS and PWLS are important differential diagnostic considerations in the clinical and genetic/chromosomal workup of these patients. Chromosomal microarrays or targeted deletion analyses using FISH or other more sophisticated genetic and chromosomal scanning methodology are required to accurately define the specific affected chromosomal zone in affected patients.

Fragile X Syndrome

While not traditionally recognized as a cause of HOS, fragile X syndrome (FXS) is an important diagnostic consideration in the spectrum of syndromic forms of genetic causes of HOS. In addition, it is even more prevalent than PWS (~1 in 4–5000) and is the most common cause of intellectual disability in boys as well as the most prevalent single *gene* identifiable cause of autism [278, 318]. Notably not all FXS patients present with the typical HOS phenotype. While FXS as an entity is associated with a greater prevalence of so-called "common" nonsyndromic obesity than age-matched unaffected children (~31% vs 18% in one series), the association with HOS occurs much less frequently (<10% of FXS patients) [318–321]. The HOS subtype of FXS has some similarity phenotypically with PWS

and has been included in some of the PWLS cohort descriptions. It is characterized by severe early-onset obesity, hyperphagia, hypogonadism, and/or delayed pubertal onset. These patients also have a higher prevalence of autism spectrum disorders than traditional FXS patients. Furthermore, they can be associated with either increased linear growth and height or short stature in addition to periorbital, axillary, and genital hyperpigmentation.

Classic/traditional FXS is the result of an expansion of the CGG repeats >200 in the 5′ untranslated region of the fragile X mental retardation 1 (FMR1) *gene*. This expansion can result either in a premutation (55–200 repeats) or a full mutation of the FMR *gene* with consequent reduced or abolished production of the FMR1 *gene* product. The expressed levels of the FMR1 *gene* product appear to correlate with the severity of the disease phenotype. The condition is typically inherited in an X-linked dominant fashion. In the patients with the HOS subtype who invariably have a PWLS presentation, there is no identifiable chromosomal deletion in the 15Q11-13 region as is typical of PWS; however, there has been demonstrated reduced expression of the CYFIP1 *gene* which is located in the same chromosome 15Q11-13 region, and the *gene* product of this *gene* is a FMR1-interacting protein.

The classic FXS syndrome is characterized by the typical so-called Martin-Bell phenotype of mental retardation, elongated face, large everted ears, developmental impairment, macroorchidism, facial dysmorphia including frontal bossing, and a range of behavioral problems including hyperactivity, impulsivity, autistic and/or autistic-spectrum features, ADHD, and also recurrent otitis media and hyperextensible finger joints. Other features of note associated with classic FXS include seizure disorder, pes planus, strabismus, scoliosis, and mitral valve prolapse [278, 320, 322–324].

Polygenic HOS

This is presumed to be a possible etiologic factor in the cause of patients with so-called "idiopathic" HOS in which no other clear cause is identifiable. It is characterized by the simultaneous presence of polymorphisms of several *genes* known from GWAS and other related studies to have an associative relationship to increased obesity risk and prevalence in population-based studies. Thus far, > than 50 distinct *gene* loci have been identified that in varying combinations and variants may contribute both to so-called "common idiopathic" obesity and less commonly to a subset of so-called idiopathic HOS. These polygenic variants individually have relatively small quantitative effects, but their multiplicity in the same patient can have multiplicative and adjunctive effects resulting in substantive additive effects. The combinatorial genetic profiles in individual patients is as expected quite variable, and the coexistence of features of the HDS identifies this group of patients as distinct from the so-called "common idiopathic" obesity as well as from other forms of HOS [202, 224, 233, 251, 325]. Of the wide spectrum of possible polymorphisms and candidate *genes*, MC4-R polymorphisms are the most prevalent with some variants associated with obesity, while others are associated with an obesity-resistant phenotype [202]. Another important candidate polygene in this regard is the FTO (fat mass and obesity-associated *gene*). GWAS studies have shown that polymorphisms especially of intron 1 of the FTO *gene* have been associated with increased obesity risk. In silico analyses of the FTO *gene* indicate that it encodes a member of the nonheme dioxygenase and 2-oxoglutarate-dependent dioxygenase superfamily of peptide products. In children, FTO polymorphisms do not seem to be associated with effects on energy intake and physical activity unlike in adults where polymorphisms have been identified to be associated with increased caloric and energy intake and reduced satiety but no obvious relationship to energy expenditure nor physical activity levels. In mice, FTO knockouts have postnatal growth retardation with reduced adipose and lean tissue mass, while transgenic FTO overexpressing mouse models are associated with increased weight with increases in both lean mass and adiposity. Other recently identified obesity-associated polygenes with familiarity from the monogenic obesity

disease arena are polymorphisms of the BDNF and POMC *genes*.

Of note, many of the obesity predisposition *genes* identified by GWAS and other related studies to be contributory to population-associated obesity risk are expressed in the CNS and most commonly in the hypothalamus highlighting the fact that beyond the extreme phenotype of HOS, hypothalamic-related dysfunction likely also plays an important role in the risk for development of the more common forms of nonsyndromic obesity.

Clinical Presentation of HOS

While patients have variable clinical presentations based on the variable etiologic factors responsible for their unique HOS state, some commonalities exist, and it is the presence of these features which when coexisting with other appropriate clinical and historical elements raises the possibility of HOS as a diagnostic consideration. Because of the heterogeneity of the causes and risk factors for HOS, it is the final common pathway of several different and unique diseases making its diagnosis a clinical one. Many of the distinctive features of hypothalamic functional anomalies are common to both HOS and HWS with the differential effects of energy balance, satiety, appetite, and body weight then distinguishing the two syndromes. As heterogenous as the causes of HOS so also are the components of this HDS cluster of clinical features and the number and combination of them that may be present in the individual patient.

Among the distinctive features of HOS are striking hyperphagia often associated with unusual food-seeking behaviors (including but not restricted to foraging for foods, stealing food, eating food from unsanitary sources and social behavior cues driven by eating opportunities). Deranged or absent satiety and overwhelming hunger are often symptom accompaniments. Reduced physical activity levels often accompany this especially in patients with craniopharyngiomas [19, 29–32].

The symptoms and features of the HDS can be categorized as shown in Table 12.6.

From a pathophysiologic perspective, HOS is often associated with hyperinsulinemia and hyperleptinemia. Other aspects of the pathophysiology of HOS that are now emerging include dysfunctional autonomic nervous system function (especially impaired sympathetic nervous system activity), melatonin dysregulation, and enhanced 11 beta-hydroxysteroid dehydrogenase 1 systemic activity [19, 29–32].

A careful and detailed history and physical examination is central to proper diagnosis of HOS and detailing of the contributing etiologic factors. Because of the heterogeneity of HOS, its management is often difficult and typically best done in a multidisciplinary fashion with collaborative interactions between the patients' pediatrician or primary care physician with a host of subspecialists including the mental health specialists (clinical psychologists and psychiatrists), neurologists, neurosurgeons, endocrinologist, and bariatric surgeon at the bare minimum. As difficult as effective weight management is even among patients with so-called ordinary common obesity, it is even more difficult among most patients with HOS and absolutely requires deployment of multimodal approach including optimization of lifestyle changes and interventions within the limitations inherent in some of these patients along with adjunctive pharmacotherapy that often requires combinatorial therapy chosen to address aspects of the identified pathophysiology in the patient. While bariatric surgery is an important adjunctive resource, it is important to realize that it is generally way less effective in this group of patients despite their degree and rapidity of weight gain often because of their distinctive underlying pathophysiology. The greatest successes thus far in HOS management have been among patients with distinctive monogenic forms like leptin deficiency that lend themselves to relatively straightforward targeted replacement therapy.

Table 12.6 Spectrum of symptom complex for hypothalamic dysfunction syndrome (HDS)

Features of the hypothalamic dysfunction syndrome (HDS) complex	
Symptom category	Spectrum
Satiety, appetite, and energy balance	Hyperphagia, reduced physical activity, anorexia, hyperactivity
Weight	Rapid-onset weight gain, morbid obesity, involuntary weight loss, wasting, cachexia
Increased intracranial pressure	Cephalgia syndromes, spontaneous emesis, visual blurring or other ocular symptoms including peripheral visual field defects, nyctalopia, progressive vision loss, etc.
Neurologic symptoms	Seizures, somnolence or hypervigilance, gait anomalies including ataxia, altered levels of consciousness, involuntary movement disorders including tremors, etc., learning defects including mental retardation, autism spectrum disorders, persistent tics, language disorders including dysarthric states, echolalia, coprolalia, stuttering, etc.
Endocrine symptom complexes	Features of hypopituitarism including amenorrhea, hypogonadism, erectile dysfunction, diabetes insipidus, chronic hyponatremia and SIADHS, central hypothyroidism, central adrenal insufficiency, growth hormone deficiency, short stature or accelerated linear growth, hyperprolactinemic symptoms including galactorrhea
Neuropsychiatric symptom complexes	Acute psychoses, manic states, personality disorders and changes, hyperdocility or hyper-aggressiveness, self-mutilatory behavior, ADHD-like symptomatology, impulsivity disorders. Mood lability, emotional lability, behavioral changes, and relationship problems
Other sexual-related symptomatology	Hypogenitalism including micropenis, infertility/subfertility, macroorchidism, precocious puberty, or delayed pubertal onset
Respiratory dysregulation	Central and/or obstructive sleep apnea, obesity hypoventilation syndrome
Temperature dysregulation	Hypo- or hyperthermic states, chills, and/or rigors
Dysautonomia	Postural hypotension, hypertensive spells, cardiac dysrhythmias; bradycardic or tachycardic states, hyper- or hypohidrosis states, flushing spells, etc.
Sleep derangement	Sleep deprivation, parosmias, narcolepsy-"like" states, hypersomnia, or hypervigilance states

Hypothalamic Wasting Syndrome (HWS)

The HWS also known as the hypothalamic cachexia-anorexia syndrome is the reciprocal/inverse manifestation of hypothalamic dysfunction to the more common HOS. For reasons that have been previously elucidated, the hypothalamic regulatory neurocircuitry for appetite, satiety, and energy balance is primarily geared at maintenance of normal weight and prevention of wasting states that significantly challenge the survival and fertility (mainly in women) imperatives of the human and other living organism's homeostatic control systems. Consequently, the defenses and redundancies built in the hypothalamic modulatory systems for prevention of wasting states are more robust that those built in to prevent caloric excess, weight gain, and obesity which had not in evolutionary terms been a major survival risk until very recently in temporal historical time lines. As a result, HWS is much less common and prevalent than HOS though not less important to appreciate and understand.

Increasing understanding of the role and basis of hypothalamic dysfunction in the etiology of wasting and cachexia associated with neoplastic and infectious/inflammatory diseases in particular has raised insight and also provided possibility for more effective management of wasting and cachetic states in general [326].

It appears that a deranged balance between orexigenic and anorexigenic signaling in the hypothalamus with attendant increase in central leptin-like signaling, increased central inflamma-

tory cytokine effects, and consequent impaired or absent adaptive caloric intake to starvation seem to underlie the development of the HWS [326–328].

Among the numerous suggested putative chemical mediators of HWS-associated cachexia and anorexia are the inflammatory cytokines tumor necrosis factor alpha (TNFα), interleukin 1 beta (IL-1β), interferon gamma (IFϒ), interleukin 6 (IL-6), and other members of the interleukin 6 superfamily of cytokine peptides such as ciliary neurotrophic factor (CNTF) and the leukemia inhibitory factor (LIF) [329–336]. These chemical mediators also appear to have a functional basis for other symptomatology known to accompany the hypothalamic cachexia-anorexia symptom complex typical of HWS including hyperpyrexia, somnolence, fever and/or chills, sleep deprivation, and deranged respiratory patterns including tachypnea and Kussmaul's and Cheyne-Stokes breathing patterns. The effects of these chemical mediators on the hypothalamic centers involved in modulating energy balance and satiety have introduced the concept of neuroinflammation as a pathogenetic mechanism for development of the clinical anorexia-cachexia phenotype associated with HWS [337–340].

While there is no clear correlation between anatomic location/topography of hypothalamic lesions and development of HWS vs HOS, comparison of similar mass lesions associated with HWS vs HOS in individual patients does suggest that more extensive lesions with more expansive CNS and hypothalamic destructive effects whether from the lesion itself or iatrogenic effects including surgery, irradiation, etc., seem to be more associated with HWS than with HOS phenotypes [35].

There is increasing evidence that the wasting associated with HWS includes both sarcopenia and adipopenia with lipoatrophy. Significant losses are observed in both the lean tissue and adipose tissue depots resulting in the clinical phenotype that resembles that associated with other cachetic wasting states such as anorexia nervosa and nutritional marasmus [328]. Better understanding of the molecular and cellular mechanisms of this process has come for animal- and human-based studies of cancer cachexia. It appears that the observed sarcopenia is the result of reduced protein synthesis within the skeletal muscles and is understood to be a prognostic indicator of increased mortality risk as well as diminished quality of life [328]. This is promoted via the ubiquitin-proteasome and autophagy lysosomal pathways in addition to the calcium-dependent enzyme system, the calpains. These cascade pathways are activated by several chemical mediators including proteolysis-inducing factor (PIF), myostatin, actin A, and a large litany of inflammatory cytokines including several of those already indicated above [328, 341–344]. These chemical mediators induce cellular cascades including the transcription factor, nuclear factor kappa B (NF-κB), reactive oxygen species (ROS), and protein kinase c. The cause of adipopenia and lipoatrophy is less well understood though a lipid mobilizing factor and the zinc alpha 2 glycoprotein (ZAG) appear to be involved [345–354]. These chemical mediators induce their adipolytic effects by several chemical pathways including increased tissue lipolysis and lipid beta oxidation caused by activation of beta 3 adrenoceptors, hormone-sensitive lipase activation, and glycerol release. There is also increased expression of uncoupling protein 1 (UCP1) in brown adipose tissue (BAT) as well as increased transition of white adipose tissue (WAT) to beige adipose tissue (BEAT) and BAT via the so-called "beiging"/browning phenomenon. The adipopenia of HWS is quite distinctive and specific with preservation of body water content and can occur in the absence of anorexia. TNFα is another important mediator of the adipopenia of HWS and mediates this effect among other means by inhibiting lipoprotein lipase expression and activity while inducing hormone-sensitive lipase expression with a net result of increased lipolysis, depletion of adipose storage stores, and inhibition of de novo lipogenesis.

There is also accumulating evidence of the role of the melanocortin central signaling pathways of the hypothalamus and the ECS in the development of the anorexia-cachexia phenotype of HWS [27, 328, 355–358]. Other important contributory elements to HWS pathogenesis

are the activation of the hypothalamo-pituitary adrenal axis of systemic inflammation and central 5HT signaling especially in the hypothalamus as a major mediator of HWS-associated anorexia [357]. It is now apparent that the hypothalamus serves both as a sensor of systemically circulating chemical mediators and amplifier and in some cases primary cause of the anorexia-cachexia phenotype of HWS. Beyond elements of the HDS, HWS in particular is typically characterized by anorexia with reduced caloric intake, increased energy expenditure (including but not restricted to increased basal metabolic rate), impaired insulin sensitivity with increased systemic insulin resistance, reduced physical activity levels, worsening anhedonia with reduced quality of life, and reduced libido with reduced sexual activity accompanying the sarcopenia and adipopenia that drive the wasting/cachexia [27, 357].

Figure 12.5 is a schematic of the established and putative hypothalamic and systemic circuitry suggested to mediate the HWS clinical phenotype.

Causes of HWS

While the prevalence of HWS is much lower than HOS, the heterogeneity of possible etiologic factors is essentially as great if not more. The common features shared by the diverse group of clinical entities that can cause HWS include the presence of clinical features of the HDS accompanied by significant relatively rapid weight loss which can be severe enough to result in clinical cachexia and which is typically the result of combined sarcopenia and adipopenia + lipoatrophy. Because of the relative paucity of reported cases of HWS, most of the published literature in this area consists of case reports and small case series [35, 299, 314, 359–395]. The fact that several of the tumors and other mass lesions described as causes of HWS are also more commonly associated with HOS argues persuasively that the exact anatomic and pathologic entity does not appear to be as critical to determining which of these clinical syndromes develop in the individual patient as opposed to possibly exact anatomical location of the lesion, extent of the disease, the

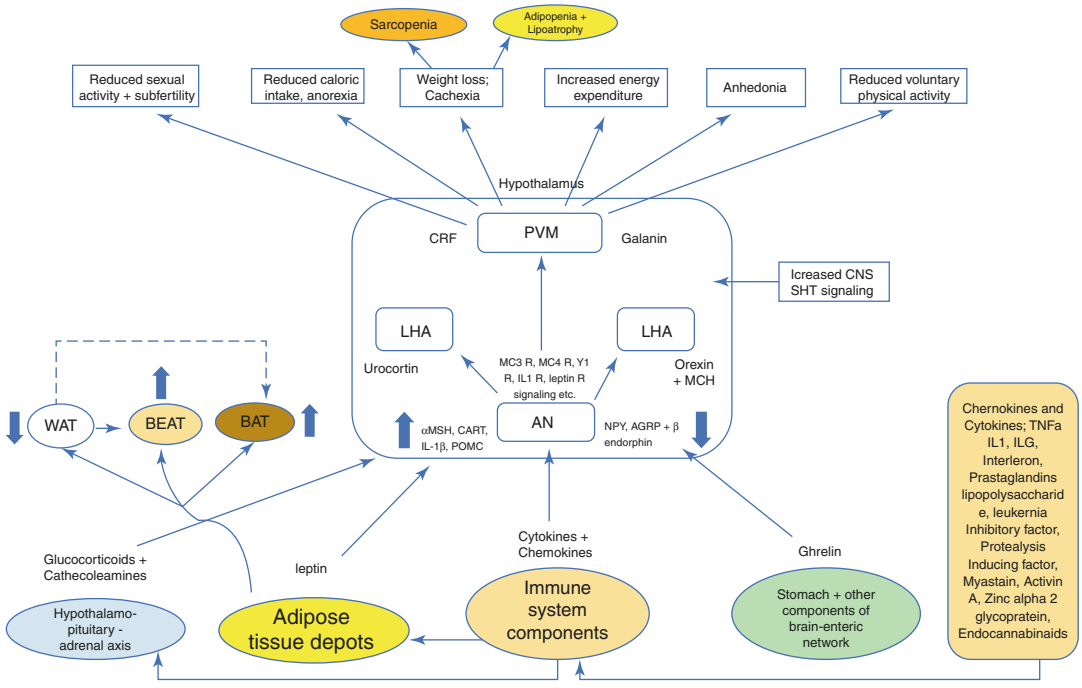

Fig. 12.5 Schematic of the neurocircuitry of systemic and neuronal mediators of HWS

exact hypothalamic nuclei and pathways disrupted by the lesion, possible genetic factors unique to the patient, and possible differences in environmental, psychosocial, lifestyle, and epigenetic interactions. Better understanding of the factors and determinants that cause such disparate phenotypic presentations from the same pathologic entity in individual patients would further expand our knowledge of the determinants and modulators of satiety, appetite, energy balance, and weight regulation. This could also result in the development of better targeted therapy for various obesity and wasting syndromes. This same dichotomy and disparity is also highlighted in the variable weight, adiposity, and growth-related clinical phenotypes associated with some chromosomal and genetic syndromes that affect contiguously close chromosomal zones and/or *genes* but result in HOS versus HWS clinical phenotypes. The PWS versus Angelman syndrome, Beckwith-Wiedemann vs Russell-Silver syndromes, and the chromosome 16P 11.2 microdeletions versus 16P 11.2 microduplication syndromes are examples of this. These relatively rare important genetic and chromosomal disorders also offer a unique opportunity for in-depth study in comparison and contrast to better understand the various genetic determinants of weight, satiety, and energy balance regulation and to better understand the bases for the various disparate phenotypic features of the syndromes. Table 12.7 provides a summary of the main identified and known causes of the HWS.

Simmonds' Cachexia

Simmonds' cachexia (aka Simmonds' disease or pituitary cachexia) is a unique clinical syndrome first described in 1914 by Simmonds and colleagues. It is a syndrome that has multiple possible underlying etiologies with the commonality of adenohypophyseal failure and associated marked cachexia [7–12, 26, 381, 382, 386]. Simmonds' original description was in the setting of postpartum adenohypophyseal necrosis following major postpartum hemorrhage and was thus a subtype of the Sheehan's syndrome [396]. Cases of Simmonds' cachexia have been described due to the broad spectrum of pathologic entities known to be associated with adenohypophyseal destruction including macroadenomas, traumatic injury, infections, inflammatory diseases (of which tuberculosis and syphilis are generally most common in the reported literature), etc. The clinical phenotype of the condition and prevalence has undergone a significant change in the decades since

Table 12.7 Summary of causes and associations with HWS

Etiologic factors for hypothalamic wasting syndrome (HWS)
Idiopathic
Empty sella syndrome, hydrocephalus
Anatomic/structural lesions
Mass lesions: craniopharyngioma, colloid cysts, Rathke pouch cyst
Tumors; germinoma, glioblastoma, chondroma, hamartoma, Langerhans cell histiocytosis (histiocytosis X), leukemia, Erdheim's tumor, meningioma, lymphoma, pituitary adenoma (invariably macroadenomas), pinealoma, teratoma, GIST tumor, pituitary carcinoma, malignant melanoma, and brain metastases.
Inflammatory mass lesions: sarcoidosis, CNS tuberculosis, arachnoiditis, encephalitis, meningitis, hypophysitis
Post-head trauma, post-neurosurgical procedures and surgery, post-cranial irradiation, post-cerebrovascular disease (stroke) including cerebral infarction and/or cerebral hemorrhage, post-pituitary apoplexy, post-subarachnoid hemorrhage, post-Sheehan's syndrome, post-anoxic encephalopathy
Cerebral aneurysms
Demyelinating syndromes: multiple sclerosis, poliomyelitis, etc.
Distinctive neuropathologic syndromes: Simmonds' cachexia, diencephalic syndrome (aka Russell's syndrome)
Genetic syndromes, including single gene mutation states and distinctive phenotype-associated genetic syndromes
Select cases of Russell-Silver syndrome, Angelman syndrome, etc.
Chemicals and pharmaceuticals
Cytokines, chemokines, and other relative bioactives; IL1, IL6, TNF, select prostaglandins and other eicosanoids, select synthetic cannabinoids, LPS, interferons, etc.

Simmonds' original description. It is certainly far less common now, and the original descriptions suggesting a female preponderance and associated "progeroid" aged appearance disproportionate to chronologic age have not been confirmed in more recent case descriptions. Notably, while these patients are typically significantly emaciated unlike other forms of HWS, they are typically not anorexic. The fact that the Simmonds' disease phenotype is far less commonly seen now even among patients with pan hypopituitarism raises speculative questions as to what the primary driver of the phenotype was/is. The possibility of the overall better nutritional status of most patients in recent times compared to the early nineteenth century, the earlier diagnosis of the underlying disease in most cases, and the general availability of multihormone replacement therapy may be the main factors explaining the secular trend changes in Simmonds' disease prevalence, severity, and reporting.

Diencephalic Syndrome

This is a rare syndrome (aka Russell's syndrome) that is usually the result of mass or other destructive lesions of the diencephalon (including the hypothalamus and thalamus). Following its original description by Russell and colleagues in 1951, the spectrum of the syndrome has been better elucidated and expanded to including a wide range of possible etiologies [28, 397–401]. Diencephalic syndrome is most commonly first described or recognized in childhood with a clinical phenotype of failure to thrive, progressive weight loss, and emaciation. Despite the cachectic clinical appearance, however, it is not uncommon for the affected children to be alert, happy, and normally interactive. Other associated common clinical features include visual anomalies, emesis, chronic headaches, and pallor. While overall neurologic development may be slowed, the affected children do typically achieve these milestones and the neurologic examination is often generally normal. While most of the children are normally behaved, some are hyperkinetic and restless, euphoric, hyperexcitable, and/or irritable [28]. Craniopharyngiomas appear to be the most commonly identified etiologic non-neoplastic mass lesions for the development of the syndrome [402–406]. Among tumors, gliomas and astrocytomas appear to be most commonly associated with the syndrome though other mass lesions like cholesterol granulomas, CNS neurofibromas in the setting of von Recklinghausen's disease (neurofibromatosis type 1), and xanthogranulomas have been described in association with the syndrome [28, 407–413]. Some patients have progressive visual decline due to optic atrophy which if not expeditiously treated can result in permanent blindness. Other features sometimes seen are secondary hydrocephalus, hypoglycemia, hyperhidrosis, and hypertension. Some cases have been described also associated with disproportionate hand and feet enlargement despite the systemic wasting [28]. While very uncommon, it is important to remember this syndrome as a potential consideration in infants, children, and even teenagers and adults who present with an otherwise etiologically unexplained syndrome of failure to thrive [28, 414, 415].

The most immediate management strategy for management of the diencephalic syndrome is the urgent diagnosis of the syndrome and pathologic identification of the etiologic mass lesion involved. Subsequent management strategies including neurosurgical resection interventions, chemotherapy, irradiation, etc., are then determined on individual case-by-case basis. Further neurosurgical interventions like ventriculoperitoneal shunting and optic chiasm decompression may be required in individual patients with urgent complications like secondary hydrocephalus and optic atrophy. Nutritional support is required for the HWS associated with the syndrome, but this tends to improve after the underlying mass lesion is appropriately treated [28, 416].

Summary Points

- The hypothalamus is central in the normal control of appetite, satiety, and energy expenditure. Hypothalamic obesity is an uncommon cause but often underappreciated cause/contributor of obesity and is often associated with

severe to morbid obesity that is typically associated with poor response to traditional intervention strategies including bariatric surgery.

- As uncommon as hypothalamic obesity is, less appreciated is the fact that hypothalamic disease may also be involved in the development of wasting syndromes or the cachexia-anorexia symptom complex.
- The underlying etiologies of HOS and HWS are variable and numerous and include tumors and other mass lesions, trauma, postradiation therapy, post-infective or post-inflammatory states, idiopathic conditions associated with neurologic lesions like neurosarcoidosis, and genetic syndromes. As our knowledge and understanding of these syndromes increase, the range of their spectrum and overall prevalence is likely to increase.
- The underlying etiologies of HOS are less variable and heterogenous than HWS with Prader-Willi syndrome and craniopharyngioma being by far the most common causes of HOS. The causes of HWS are way more variable making the understanding of the underlying pathophysiology more difficult. This is further compounded by their much lower overall prevalence.
- There are some commonalties as regards etiologic factors responsible for the development of HOS and HWS such as certain mass lesions like craniopharyngiomas, tumors like germinomas and teratomas, and various infective and inflammatory neurologic diseases. A better and fuller understanding of these conditions and the factors and determinants of why they cause HOS in some patients but HWS in others is an important area of investigation to enable better understanding of the control and regulation of energy balance and weight management which could also translate to better therapeutic and management options for both of these syndromes and potentially for other forms of obesity and wasting clinical states.
- The dramatic clinical response of leptin replacement in managing the clinical phenotype of leptin-deficient obese subjects raises the prospect for precision treatment options for some forms of HOS and possibly HWS with underlying genetic basis. The existence of some dichotomous genetic syndromes like PWS and Angelman syndrome, Russell-Silver and Beckwith Wiedemann syndromes, and the 16P 11.2 microdeletion vs microduplication syndrome offers the opportunity for in-depth study of candidate *gene* and chromosomal zone mutations and their disparate effects of weight, satiety, appetite, and energy balance and could help identify potential targets for targeted pharmaceutical intervention and thus more effective long-term management.
- Because the underlying mechanisms for the development of both hypothalamic obesity and wasting syndromes are numerous and variable, the effective management is difficult, typically does not respond to traditional intervention strategies, and does not respond well to mono-therapeutic interventions.
- Careful study of the anatomical location of lesions, the disrupted neurocircuitry, and the consequent abnormal neuroendocrinology and neuro-signaling associated with HOS vs HWS is important in better understanding of why some entities like craniopharyngiomas can be associated with marked obesity in most patients but normal weight status or profound wasting syndromes in other patients. Such knowledge could help anticipation, prevention, prognostication, and effective management of weight derangements in patients with such hypothalamic lesions.

Concluding Remarks

- HOS and HWS are uncommon but important causes of obesity and wasting. HOS is significantly more prevalent than HWS.
- Prader-Willi syndrome and craniopharyngioma are the most common etiologies for HOS worldwide, while the causes of HWS are more variable and diverse.
- Both HOS and HWS are typically resistant to traditional weight management interventions and need careful phenotypic and genotypic

(when indicated) characterization to guide plans for long-term management.

- Multiple adjunctive, multidisciplinary management strategies have far better potential for success in these conditions than simple monotherapy or isolated attempts at lifestyle or behavioral changes.
- Greater awareness of these entities and more careful clinical, metabolic, phenotypic, and genotypic study and cataloging of patients with HOS and HWS are sorely needed. Careful, detailed registry and natural history studies of cohorts of these patients in addition to well-designed treatment trials are also needed to improve the long-term management of these patients and improve their long-term prognosis.
- In view of the relative rarity of these syndromes and the heterogeneity of their causes, the best means of study will require multicenter and multinational collaborations to evaluate various combinatorial and novel pharmacotherapeutics along with better established lifestyle, behavioral, and medical interventions. It is likely that the knowledge derived from these sorts of studies will provide insights that can then be applied to the more common so-called "ordinary" common obesity and wasting syndromes.

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Hypothalamic Sleep Disorders

13

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Over the past 90 years, evidence that the hypothalamus is a critical site in regulating sleep and wakefulness has grown. While at first scientists thought that sleep was simply the absence of being awake, that view changed markedly. Both sleep and wake states are active processes. In addition, as the pathways regulating sleep and wakefulness were unmasked, important communication of the brainstem and spinal cord with the hypothalamus emerged. At the same time, clinical disruption of sleep does not easily enable pinpointing *where* and *how* specific clusters of neurons alter sleep. While substantive roles of the hypothalamus in phases of sleep are recognized, expansive intrahypothalamic connectivity and extrahypothalamic influences within the hypothalamus bring diverse environmental influences to the hypothalamus. A good example is that obesity can be the source of sleep problems and short sleep can alter food intake to produce obesity [1–3]. The interactions among metabolic disorders, weight homeostasis, and sleep are described in [3]. These can make interpreting primary versus secondary hypothalamic involvement difficult. Knowledge of pathways coursing through the hypothalamus can alter interpretation of whether altered sleep is the result of resident cell injury versus interruption of thoroughfares. Lastly, disruption of hypothalamic systems can affect sleep even though little is known of how these systems interact with sleep centers. This chapter will review hypothalamic systems that have a direct impact on sleep, wakefulness, or regulation of timing and examine disorders involving lesions, stress, global warming, and aging that affect sleep.

Hypothalamic Neurons That Govern Sleep

Physicians first became aware that hypothalamic systems could affect sleep (causing or disrupting it) when they encountered patients with lesions positioned within the hypothalamus and noticed effects on sleep. Formal research merged information from targeted lesion studies [4], drug effects (or side effects) [5], changes in sleep patterns across the life span [6, 7], or genetic disorders involving sleep [8, 9]. As transmitters implicated for sleep regulation were defined, manipulations of select transmitter systems and documentation of neuronal activity within select populations of neurons when sleeping or awake began to define how the brain controlled sleep. Together, circuits controlling sleep and wakefulness have led to an understanding of the interactions of functional paths, and many involve the hypothalamus or related forebrain systems.

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Figure 13.1 illustrates the hypothalamic and basal forebrain systems that participate in the regulation of sleep and wakefulness (modified from [10]). Yet, consideration of the role the hypothalamus plays in sleep and wakefulness cannot be viewed in isolation of the brainstem reticular formation. As Fig. 13.2 shows, the reticular formation not only projects to the cortex but

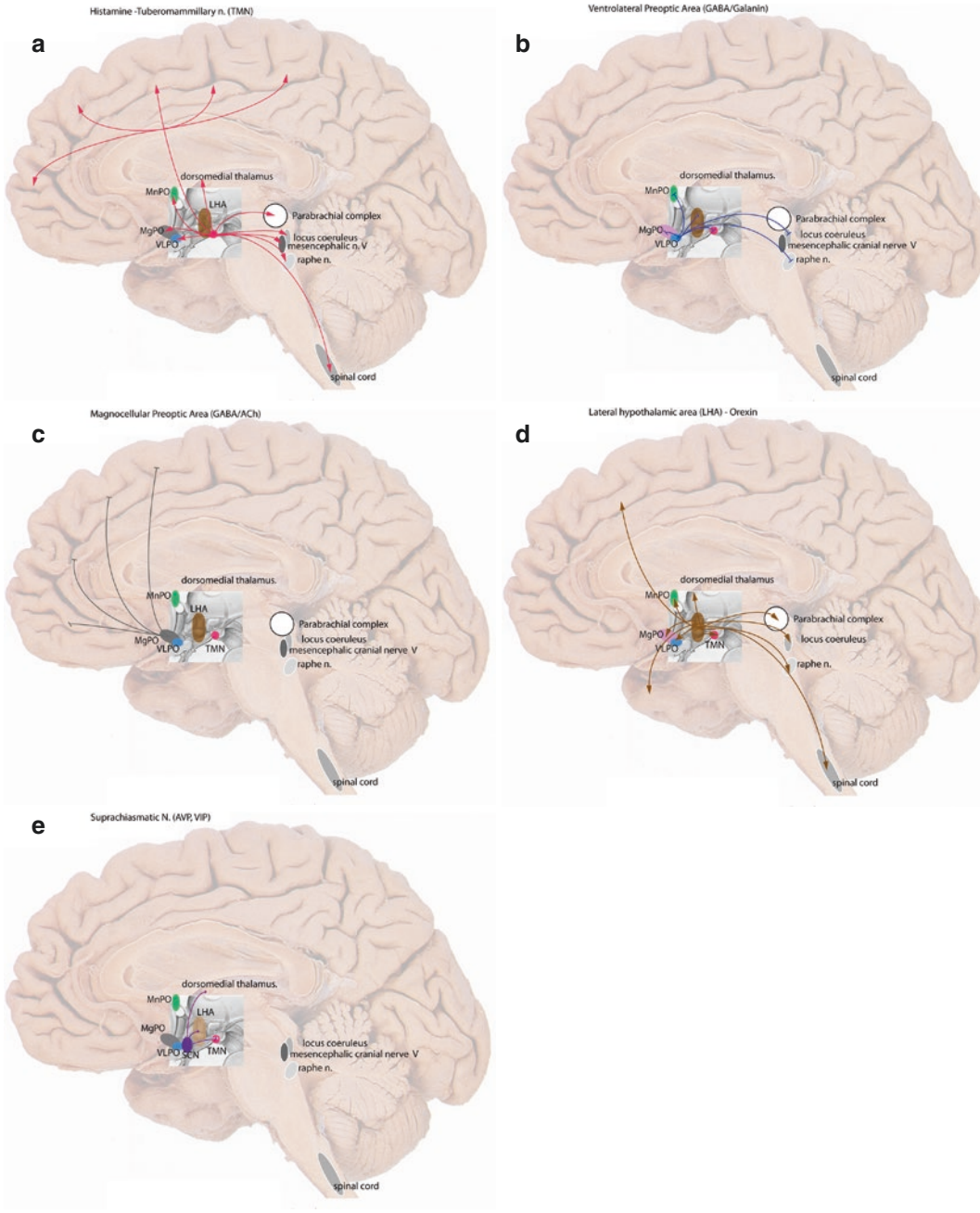

Fig. 13.1 Hypothalamic systems with a role in regulation of sleep and wakefulness (From [10]). (**a**) Pathways of histamine neurons of the tuberomammillary nucleus; (**b**) the ventrolateral preoptic area, VLPO, GABA, galanin, and adenosine neurons; (**c**) the magnocellular preoptic area GABA neurons; (**d**) the lateral hypothalamic area (orexin/hypocretin and melanocyte concentrating hormone neurons); (**e**) the suprachiasmatic nucleus. (With permission from Nova Publishing)

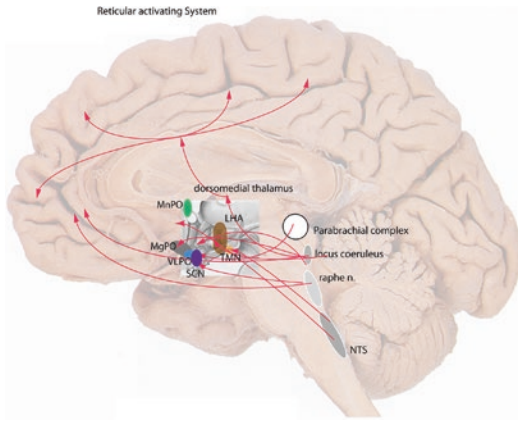

Fig. 13.2 The brainstem reticular activating system and its connections. Schematic of the projections from the reticular formation to the hypothalamus and cortex. (Hoffman, unpublished)

includes connections with hypothalamic areas, many of which display reciprocal projections to the reticular formation and the same cortical areas innervated by the brainstem systems. Tied to the regulation of sleep and wakefulness, the reticular formation is important for matters of arousal and consciousness, and in some ways, these can diverge from simply being awake. Discussion of sleep walking highlights this feature. Individuals asleep in terms of awareness of their environment move and perform tasks normally found when they are awake. Monitoring of EEG signals also illustrates how cortical activity is not simply "on" or "off" when awake vs. asleep. Moreover, as a site for control of autonomic functions (temperature, cardiovascular function, gut motility, sympathetic tone), timing through the biological clock in the suprachiasmatic nucleus, emotional responses, and neuroendocrine function (reproduction, growth, corticosteroid stress control), the hypothalamic systems can modify activity from any or all of those systems to then regulate arousal, consciousness, and sleep. As a result, disease processes involving the hypothalamus can be highly varied in effect and affect the network of neurons that produce the observed effects rather than only one population.

The selective neuron populations within the hypothalamus with defined roles in sleep are neurons of the *posterior hypothalamus* that express histamine, adenosine, and sometimes GABA [Fig. 13.1a], neurons of the *preoptic area or basal forebrain* that express glutamate, GABA (alone or with galanin) in the ventrolateral preoptic area (VLPO) (Fig. 13.1b), acetylcholine or GABA alone in the magnocellular preoptic area [Fig. 13.1c], and neurons of the *lateral hypothalamus* that express hypocretin/orexin and melanocyte concentrating hormone (MCH) (Fig. 13.1d). In the anterior hypothalamus, the suprachiasmatic nucleus, SCN, is positioned to receive direct retinal projections and a long history of involvement in sleep (Fig. 13.1e).

Histamine has a long history of participation in wakefulness stemming from intracerebral injections in animals [11], use of drugs that block histamine's receptors [12], and later genetic manipulation of animals to knockout expression of histidine decarboxylase [13], the rate-limiting enzyme for histamine synthesis. As functional MRI studies improved in resolution, histaminergic-rich regions show elevated activity in insomnia, furthering the case for histamine in wake states and changes in that system when sleep is disrupted [14].

In the forebrain at the junction of the preoptic area and hypothalamus are two noteworthy cell populations that participate in sleep. One is in the ventrolateral preoptic area (VLPO). These cells express GABA along with a peptide and galanin and are active during sleep [15]. Not surprisingly, lesions of this region produce chronic insomnia in both humans [16, 17] and animals [18]. The second is the magnocellular preoptic area where the neurons express GABA. The cells are wake-active [19]. The GABA neurons of the magnocellular preoptic area are linked to arousal through disinhibition of inhibitory cortical systems. Their main target is the GABA neurons of the prefrontal cortex, and increased activity of these cells affects arousal by inhibiting the GABA neurons in the cortex that would normally dampen arousal. When those neurons are overstimulated through knockout of an inhibitory channel ($K_V2.2$), subjects show increased wakefulness and the GABA neurons have elevated enzymes

synthesizing GABA (GABA decarboxylase, or GAD) [19], and the prefrontal and cingulate cortex shows marked signs of neuron activation (Hoffman, unpublished).

Neurons of the suprachiasmatic nucleus (SCN) that express vasopressin and VIP are important for the entrainment of multiple brain activities by the light: dark schedule. Studies of SCN function in animals make clear that the timing of sleep and wakefulness is largely dependent on an inherent mechanism within SCN neurons modified by transmission of retinal signals to the hypothalamus that shift the activity of those cells to match the light: dark pattern. The processing of those stimuli to the brainstem, to the pineal gland where melatonin is synthesized, and to the neurons of the posterior and anterior hypothalamus set behavioral activity patterns. The perceived importance of the SCN is illustrated by the commentary by Dr. Christopher Muth who stated: "sleep-wake disorders occur when the body's internal clock does not work properly or is out of sync with the surrounding environment" [20]. On a larger scale, scientists have divided sleep problems into two main domains: clocks and homeostatic pressure. Yet, in some ways, neither makes simple the determination of where sleep problems are initiated. As will be seen in the subsequent discussion, hypothalamic involvement in some sleep disorders is likely even if the precise cell population prompting the disorder is difficult to pinpoint. For others, the initiating site is clear.

Blindness prevents light from entraining SCN rhythms, and this can lead to a phenomenon called free-running rhythms in which the SCN's own inherent rhythm is either longer than 24 h or shorter, and thus each day the sleep/wake cycles shift away from ambient light. Blindness is not universal in altering sleep timing. Of blind subjects, 37–40% do not exhibit free-running sleep/wake rhythms [21]. Other stimuli can entrain the clocks. Among them are feeding and activity. Localized lesions of the SCN behave differently. Without the clock in the SCN, sleep and wake appear random and fragmented with loss of clear consolidated sleep [22], a feature strikingly different from the lack of light transmission to the SCN. Indeed, a subject with a discrete lesion of the SCN from a gunshot wound [22] displayed a highly irregular pattern of sleep-wake behavior with no regular distinct bouts of sleep. That pattern is similar to that observed in animals with SCN lesions.

How the SCN dictates circadian rhythms when light dark cues change is leading to evidence of a very different role for the biological clock in the SCN. Early studies of SCN function had proposed that the SCN-linked light cues drive behavioral rhythms. They are integrated with clock gene activity in both the SCN and its targets, and this drives the behaviors. Vasopressin is one of the key output transmitters of the SCN, and its expression varies with the time of day. Initially, it was thought that if an external cue changed, vasopressin would shift the timing of the clock. For example, jet lag or shift work affects clock rhythms, and the changes are determined by the magnitude and direction of change in cues. Yet the clock does not quickly change in response to the environment. It can take days to shift activity rhythms either forward or backward. One would think that if the SCN prompts clock changes, going to a different functional time zone would immediately alter behavioral rhythms. Yet the intact SCN does not immediately change the clock functions. Rather, the absence of vasopressin receptors [23] prompts immediate time shifts, suggesting that the SCN is attempting to *maintain* rather than *drive* clock changes. In addition, investigators have suggested that SCN connections to sleep-wake control regions are indirect due to the paucity of data showing SCN innervation of hypothalamic regions known to regulate sleep [24–26]. One possibility is that examination of SCN efferents may not have considered all the candidates. For example, early studies did not include the tuberomammillary region of the posterior hypothalamus where histamine neurons reside. More recent data show the tuberomammillary region is a target of SCN efferents [27]. Furthermore, while the orexin/hypocretin systems are now found to receive SCN input, those systems had not been known when the tract-tracing studies were conducted.

A second neuronal population with a well-defined role in sleep is the orexin/hypocretin neurons of the lateral hypothalamus. Understanding of their role in sleep has stemmed from narcolepsy, a condition where the orexin/hypocretin neurons are destroyed by autoimmune processes that selectively destroy those neurons [28–33]. Figure 13.3 [33] shows the localization of orexin/hypocretin in a normal human subject and an individual who was narcoleptic. Figure 13.4 illustrates the change in pattern of sleep/wake behavior in a normal individual and one with narcolepsy adapted from [34]. Narcolepsy, while presenting with interruption of wake periods at night and sleep during the day, also displays premature entry from wake to REM sleep not found in normal subjects. In narcoleptics, sleep can be triggered by reward stimuli or by emotional states that would normally trigger arousal. In animals, forms of narcolepsy from genetic deficits in orexin/hypocretin [35–37] display similar sleep disturbances to those seen in narcoleptic humans, reinforcing the selectivity of the autoimmune responses in targeting the orexin/hypocretin cells.

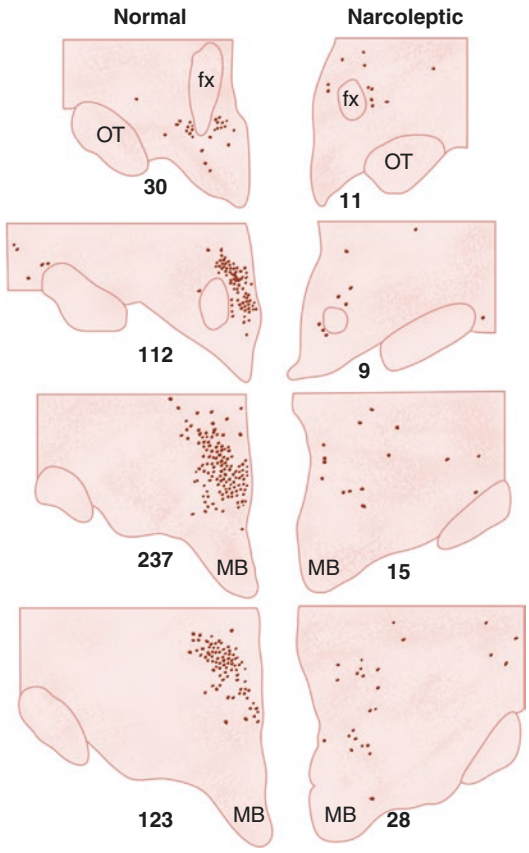

Fig. 13.3 Plots of orexin/hypocretin neurons in the hypothalamus of (**a**) a normal subject and (**b**) a narcoleptic subject. (From [33] with permission from Neuron)

Moreover, SCN lesions can produce alterations in orexin cells, raising the possibility that some disturbances initiated by the SCN might produce their disruptions in sleep from disturbing orexin/hypocretin. At the same time, examinations of narcoleptic subjects have been associated with changes in histamine, but it is unresolved if histamine dynamics are reduced or enhanced. Examination of spinal CSF levels of histamine shows a reduction in narcoleptic patients [38–40]. This suggests that stimulation of histamine neurons is low at the time of sampling or that changes in histamine release are not immediately reflected by lumbar sampling of CSF; however, examination of the potential to synthesize histamine by examining expression of the rate-limiting enzyme histidine decarboxylase, HDC, shows elevated expression in the tuberomammillary hypothalamic neurons of narcoleptic subjects [41]. Moreover, studies have questioned whether CSF histamine levels accurately reflect the secretory activity of the hypothalamic neurons and raise concerns over the interval between stimulus and spinal sample acquisition as one feature making interpretation of data difficult [42]. When samples were obtained from the cisterna magnum, significant changes in wake behavior and histamine levels were observed [43]. It may be that the intermittent sampling confounds interpretations of the overall activity of the histamine cells due to lags in CSF level changes. By contrast, in monoaminergic systems, increased synthetic enzyme levels are tightly linked to stimulatory drive. The blockade of inhibitory signals to GABA neurons through knockout of a potassium channel $K_V2.2$ produces elevations in GAD in the magnocellular preoptic area neurons [19] that were overstimulated. Long-term sleep deprivation (up to 5–20 days of duration) produced increased HDC expression in rodents [Fig. 13.5] [44] that explains the brief manic behavior seen when animals are removed from sleep depri-

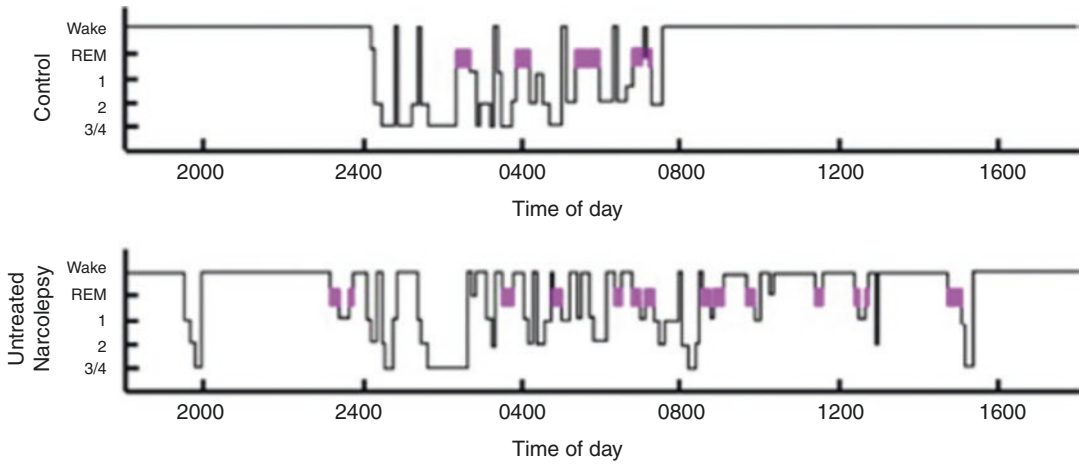

Fig. 13.4 Somnograms of a (**a**) normal subject and (**b**) a subject with narcolepsy. From (http://healthysleep.med.harvard.edu/image/429?height=80%). (No indication of where to go for permission to use figure)

vation chambers and placed in home cages and may underlie the noted changes in mania in bipolar subjects [45]. Expression of orexin/hypocretin is also elevated upon chronic sleep disruption [46] and with the changes in HDC may help to explain the irregular sleep/wake behavior noted upon termination of the stimuli to stay awake. These features illustrate how hypothalamic systems are affected and adapt in response to changes in neuronal activity when sleep is chronically disturbed.

Disorders of sleep are commonly observed as people age. While it is well accepted that aging affects hypothalamic function to produce these changes, studies of human hypothalamus had first suggested that vasopressin neurons of the SCN, which show variation during day- and nighttime in transmitter expression in young subjects, were lost in aging [47]. Yet the simple view that the SCN is responsible for age-related sleep problems is being challenged. Studies that use anatomical measures of the brain sleep/wake systems can lose the power of the relationship between neuronal numbers and sleep behavior if only mean values are used. The use of regression analyses provides a solution to that problem. In examining sleep patterns and then comparing them to postmortem changes in the brain, age-dependent losses of ventrolateral preoptic area GABA/galanin neurons accurately predict the magnitude of sleep dynamics seen prior to death in those subjects without Alzheimer's disease [16]. Those subjects had no significant change in SCN neurons linked to sleep dynamics. A number of reviews have discussed how activity within select neuron populations varies during the phases of sleep [48, 49]. While an important consideration in determining which neuron populations might be causing sleep alterations, it is also important to understand that many of these populations of cells adjust when a change in sleep occurs as discussed above for changes in histamine, orexin, and markers of GABA neurons. In analyzing transmitter systems in the hypothalamus to evaluate their roles in dictating sleep changes, the scientific community is only beginning to incorporate the network properties of hypothalamic systems that can affect sleep and move away from attempts to ascribe sleep disruption to only one system.

The hypothalamus does much more than simply regulate the biological clock and sleep and wake states. Recent discussions of hypothalamic systems have emphasized their interconnections and focused on those regions that regulate endocrine function, body temperature, autonomic functions, and complex behaviors such as food intake in addition to sleep and circadian rhythms.

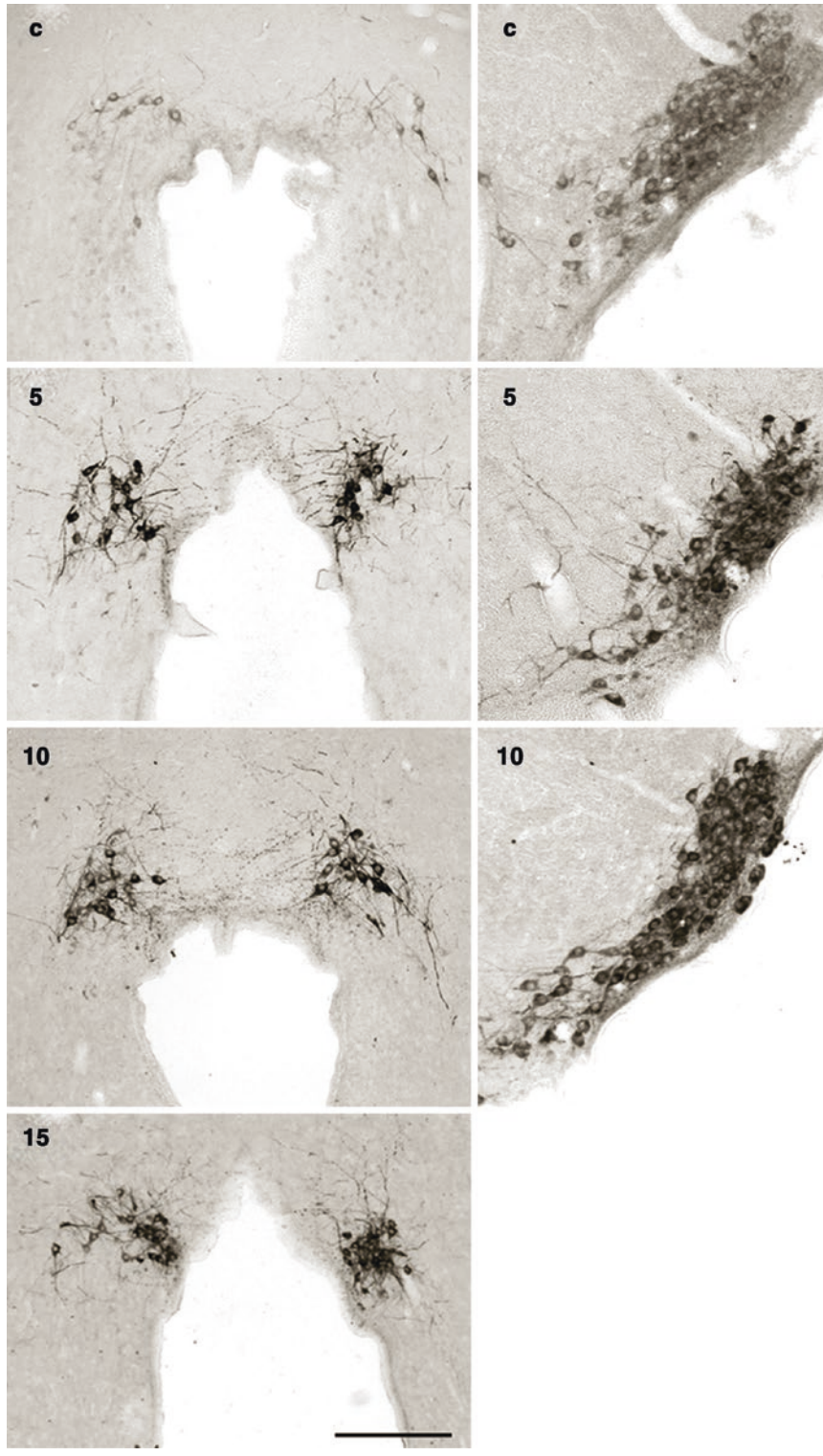

Fig. 13.5 Increased immunoreactivity for histidine decarboxylase in rats that were maintained in their home cages (0 days sleep-deprived) or REM sleep deprived for 5, 10, or 15 days. (From [44]. No permission needed)