2.1 A Brief Historical Overview

An English scientist, Geoffrey Harris first seriously urged the idea that the brain controls the pituitary gland through chemical mediators [1]. He supposed that the cells of the hypothalamus might synthesize pituitary-controlling hormones and release them into nearby blood vessels, which reach and distribute the Turkish saddle. Harris showed that cutting of the portal vessels impedes the pituitary hormone production. However, it was not until discoveries of the hypothalamic hormones by Guillemin and Schally that Harris’s theory was proved. Hypothalamic hormones, which are secreted by the hypothalamic neurons and regulate the anterior pituitary hormones (Table 2.1), were mostly discovered by two competitive researchers, Dr. Roger Guillemin and Dr. Andrew Schally [1–3]. Thyrotropin-releasing hormone (TRH), a peptide consisting of three amino acids, was the first-identified hypothalamic hormone [4, 5]. The discovery of the hypothalamic hormones was followed by luteinizing hormone-releasing hormone (LH-RH or gonadotropin-releasing hormone; Gn-RH) [6], somatostatin [7], and growth hormone-releasing hormone (GH-RH) [8, 9].

The search for hypothalamic hormones by Dr. Guillemin and Dr. Schally was so competitive that it was called “the Nobel Duel.” Both the research groups had aimed at the discovery of corticotropin-releasing hormone (CRH), a hypothalamic hormone which is secreted by the stimuli of “stress” and releases adrenocorticotropic (ACTH) from the anterior pituitary, but without success. Although both Dr. Schally and Dr. Guillemin were endowed with the Nobel Prize in 1977 [1–3], the identification of CRH had to await the isolation of CRH from the ovine brain by Vale et al. [10] and the subsequent molecular cloning of human CRH gene by Shibahara et al. [11].

Another recent advance in the hypothalamic research has been promoted by the discovery of leptin, a peptide hormone secreted by the adipose tissue [12]. Leptin acts on the brain, in particular, on the hypothalamus and suppresses appetite. Moreover, leptin controls the energy expenditure centrally. Thus, a novel endocrine axis, the adipocyte-hypothalamic axis, has been revealed. It has been shown that several neuropeptides in the hypothalamus, including neuropeptide Y (NPY), melanin-concentrating hormone (MCH), and α-melanocyte-stimulating hormone (α-MSH), regulate the appetite and some of these neuropeptides appear to be under the control of leptin. Furthermore, some gut hormones act on the brain as circulating hormones or via the vagal nerve, and regulate the appetite. For example, ghrelin secreted from the stomach stimulates the appetite [13, 14], whereas peptide YY (PYY) secreted from the intestine suppresses it [15]. Some types of obesity are caused by genetic abnormalities in these hormones, neuropeptides, their receptors, and processing enzymes. Obesity is closely related to the pathogenesis of hypertension, diabetes mellitus, and atherosclerosis, and is therefore one of the major concerns in medical care in the twenty-first century. Thus, the hypothalamus appears to play a key role in the pathogenesis of many common diseases, including obesity.

2.2 Physiology and Anatomy of the Hypothalamus

The hypothalamus plays essential roles in the central regulation of hormone secretion in most of endocrine organs, as well as a variety of autonomic functions such as the regulation of appetite, reproduction, temperature, water-electrolyte metabolism, circulation, emotional states, and sleep. The hypothalamus is located at the basal area of brain between the optic chiasm (anteriorly), and the mamillary body and the posterior commissure (posteriorly) (Fig. 2.1). The lateral border is the internal capsule and the basis pedunculi. The dorsal limit of the hypothalamus is the horizontal.
level of the hypothalamic sulcus on the medial wall of the third ventricle, roughly at the horizontal level of the anterior commissure. The median eminence forms the floor of the third ventricle and constitutes the infundibulum. The hypothalamic neurons transport hypothalamic hormones by the axonal transport and release them into the capillaries of the primary plexus of the hypophyseal portal system at the median eminence. The hypothalamic hormones reach the anterior pituitary lobe via the hypophyseal portal system, and regulate the secretion of the respective anterior pituitary hormones. On the other hand, two posterior pituitary hormones, vasopressin and oxytocin, are produced in the magnocellular neurons of paraventricular and supraoptic nuclei, transported to the posterior pituitary lobe via the axonal transport (Fig. 2.2), and released into the systemic circulation. The pituitary (hypophysis) is attached to the infundibulum.

The hypothalamus has mainly two roles in the endocrine regulation: (1) the production and secretion of hypothalamic hormones (Table 2.1), which regulate the secretion of anterior pituitary hormones from anterior pituitary lobe, and (2) the production of two posterior pituitary hormones, vasopressin and oxytocin. Hypothalamic hormones are

<table>
<thead>
<tr>
<th>Hypothalamic hormones</th>
<th>Abbreviations</th>
<th>No. of amino acids</th>
<th>Target pituitary hormones</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticotropin-releasing hormone</td>
<td>CRH</td>
<td>41 amino acids</td>
<td>ACTH</td>
<td>(+)</td>
</tr>
<tr>
<td>Growth hormone-releasing hormone</td>
<td>GH-RH or GRH</td>
<td>40 or 44 amino acids</td>
<td>GH</td>
<td>(+)</td>
</tr>
<tr>
<td>Somatostatin (growth hormone-release inhibiting hormone)</td>
<td>Gn-RH or LH-RH</td>
<td>14 or 28 amino acids</td>
<td>GH and TSH</td>
<td>(−)</td>
</tr>
<tr>
<td>Gonadotropin-releasing hormone (Luteinizing hormone-releasing hormone)</td>
<td>TRH</td>
<td>3 amino acids</td>
<td>TSH and prolactin</td>
<td>(+)</td>
</tr>
</tbody>
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(+), stimulatory effects; (−), inhibitory effects

Fig. 2.1 (a) Magnetic resonance imaging (MRI) of the brain of a normal subject, and (b) the approximate positions of the hypothalamic nuclei. OC optic chiasma; AP anterior pituitary lobe (adenohypophysis); PP posterior pituitary lobe; Inf infundibulum; MB mamillary body; SCN suprachiasmatic nucleus; AN anterior nucleus; PA preoptic area; PVN paraventricular nucleus; DMN dorsomedial nucleus; PN posterior nucleus; VMN ventromedial nucleus; InfN infundibular nucleus (arcuate nucleus); SON supraoptic nucleus (After Carpenter MB, Sutin J. Human Neuroanatomy, 8th edit. Baltimore/London: Williams and Wilkins 1983.)

Fig. 2.2 Immunocytochemistry of arginine vasopressin in the human hypothalamus. Vasopressin immunoreactive cell bodies are located in the paraventricular nucleus (PVN) and supraoptic nucleus (SON). Arginine vasopressin-positive nerve fibers (AVP-NF) run from these nuclei toward the infundibulum (Inf) and the pituitary stalk. 3rd V the third ventricle; OT optic tract (Reproduced from Takahashi K, Murakami O, Satoh F, Mouri T. The hypothalamus and neurohypophysis. In: Stefanaceu L, Susano H, Kovacs K, eds. Molecular and Cellular Endocrine Pathology. London: Arnold, 2000:45–74, with permission.)
Hypothalamic hormones include the following five peptide hormones: corticotropin-releasing hormone (CRH), growth hormone-releasing hormone (GRH or GH-RH), somatostatin (growth hormone-release inhibiting hormone), gonadotropin-releasing hormone (Gn-RH or luteinizing hormone-releasing hormone LH-RH), and thyrotropin-releasing hormone (TRH) (Table 2.1). These hypothalamic hormones are produced in the cell bodies of neurons located in the hypothalamus and transported through nerve fibers by the axonal transport to the median eminence (Fig. 2.3). Hypothalamic hormones are also produced in other brain regions and may act as neurotransmitters or neuromodulators. For example, TRH has been shown to have neurotransmitter actions; it increases locomotor activity, increases body temperature, causes trembling behavior, and decreases food intake, when administered centrally [19].

In addition to these hypothalamic hormones, a number of bioactive substances are involved in the regulation of anterior
pituitary hormone secretion [20]. These include classical neurotransmitters (e.g., noradrenaline, dopamine, acetylcholine), excitatory amino acids (e.g., glutamic acid), various neuropeptides (e.g., kisspeptins [21], neuropeptide Y(NPY), calcitonin gene-related peptide (CGRP) (Fig. 2.5), vasoactive intestinal polypeptide (VIP), pituitary adenylate-cyclase-activating polypeptide (PACAP), (Fig. 2.6), substance P and endothelin-1, and bioactive gas molecules (e.g., nitric oxide (NO) and carbon monoxide (CO)). These regulatory substances (1) act on the neurons in the hypothalamus and regulate the production and/or secretion of hypothalamic hormones, (2) are released into the portal vessels, and modulate the actions of hypothalamic hormones on the anterior pituitary lobe, and (3) are produced in the anterior pituitary cells and act as paracrine or autocrine regulators in the anterior pituitary hormone secretion.

2.3.1 CRH

CRH is a 41-amino-acid peptide originally isolated from the ovine hypothalamus [10]. Human CRH is identical to rat CRH, but the structure of human CRH differs in 7 amino acids from that of ovine CRH [11]. The production and secretion of CRH in the hypothalamus are regulated by the negative feedback mechanism of ACTH from the anterior pituitary and cortisol from the adrenal cortex. Inflammatory cytokines, noradrenaline and neuropeptides, such as NPY, also have effects on the production and secretion of CRH in the hypothalamus.

In human hypothalamus, CRH is localized in the parvocellular neurons of the paraventricular nucleus (Fig. 2.3) and is co-localized with arginine vasopressin in these neurons (Fig. 2.4) [16]. It is known that a stimulatory effect of CRH on the ACTH secretion is potentiated by vasopressin. In experimental animals, adrenal insufficiency due to adrenalectomy causes increases in the expression of CRH and vasopressin in these neurons, which are suppressed by glucocorticoid supplement. Patients with primary or secondary adrenal insufficiency often show a defect in water excretion accompanied by hyponatremia and elevated plasma vasopression levels. Increased production of vasopressin in the parvocellular neurons may account for the pathogenesis of hyponatremia in these patients.

CRH is present not only in hypothalamus but also in extra-hypothalamic brain areas and peripheral tissues, such as adrenal medulla and gastrointestinal tract. CRH may act as a neurotransmitter or neuromodulator in the brain, for example for the regulation of appetite regulation and emotion in various aspects of stress. There are at least three other
members in the CRH family peptides: urocortin, stresscopin-related peptide (urocortin II) and stresscopin (urocortin III) [23–25], which are described in the section, 2.3.6 Receptors for hypothalamic hormones and their mutation.

2.3.2 GH-RH and Somatostatin

Growth hormone (GH) in the anterior pituitary is regulated by two hypothalamic hormones: the releasing hormone is growth hormone-releasing hormone (GH-RH or GRH), and the release-inhibiting hormone is somatostatin.

GH-RH was isolated from the tumor tissue of a pancreatic islets cell tumor in a patient with acromegaly [8, 9]. Two major forms were found: a 44-amino-acid peptide and a shorter 40-amino-acid peptide identical to the N-terminal 40 amino acids of GH-RH (1-44), both of which are also found in the hypothalamus. Somatostatin is a 14-amino-acid peptide that was isolated from sheep hypothalami in the search for the hormone responsible for stimulating the release of GH from the anterior pituitary [7]. Somatostatin inhibits the secretion of both GH and TSH from the anterior pituitary lobe. A larger molecular form of somatostatin consisting of 28 amino acids (somatostatin-28), a precursor of somatostatin-14, is also present. Somatostatin-14 corresponds to a C-terminal 14-amino-acid portion of somatostatin-28.

GH-RH immunoreactive cell bodies and somatostatin-immunoreactive cell bodies are found in the infundibular nucleus of the human hypothalamus [26, 27], whereas these two peptides are not co-localized in the same neurons. GH-RH containing cell bodies are localized in an area more dorsal than that of somatostatin-containing cell bodies. GH-RH and somatostatin are also expressed in the extra-hypothalamic brain areas and peripheral tissues, such as gastrointestinal tract, pancreatic islets and adrenal medulla.

In addition to GH-RH and somatostatin, a number of factors such as free fatty acids, acetylcholine, amino acids, opiates, glucocorticoids and some neuropeptides also have direct or indirect effects on GH release. GH secretagogues were discovered as a series of small peptide derivatives of Met-enkephalin, which selectively stimulated GH secretion from pituitary cells [28]. GH secretagogues act via a specific G protein-coupled receptor: the GH secretagogue receptor [29], not via the GH-RH receptor. Ghrelin is a recently discovered endogenous ligand for GH secretagogue receptor [13]. Ghrelin is a 28-amino-acid peptide with an octanoyl group on the third N-terminal amino acid serine, and is expressed in the arcuate nucleus of hypothalamus and the endocrine cells of stomach. Appetite-stimulating actions of ghrelin are described in the later section 2.12 “Appetite regulation, obesity, and anorexia nervosa.”

2.3.3 Gonadotropin-Releasing Hormone (Gn-RH) (Luteinizing Hormone-Releasing Hormone LH-RH)

LH-RH is a 10-amino-acid peptide that stimulates secretion of two gonadotropins: luteinizing hormone (LH) and follicle stimulating hormone (FSH), from the anterior pituitary [6]. Therefore, LH-RH is also called gonadotropin-releasing hormone (Gn-RH). The Gn-RH precursor generates another peptide called Gn-RH-associated peptide (GAP). GAP stimulates gonadotropin release from the rat’s anterior pituitary cells in culture [30].

Gn-RH-expressing neurons migrate during development from their birth place on the medial side of the olfactory plaeode into the brain [31]. In the adult hypothalamus, Gn-RH-positive cell bodies are most numerous in the ventral and basal hypothalamus [32]. Gn-RH-positive cell bodies extend ventrally as far as the median eminence and infundibular stalk and caudally as far as the mammillary complex. Gn-RH positive nerve fibers were observed in the median eminence and the organum vasculosum of the lamina terminalis. A large proportion of Gn-RH fibers continue uninterrupted through the internal zone of the median eminence and infundibular stalk to enter the posterior pituitary. Gn-RH positive nerve fibers project to the posterior pituitary, but the physiological roles of Gn-RH transported to the neurohypophysis remain to be determined. In addition, there are extra-hypothalamic projections of Gn-RH fibers to the habenular complex, the amygdaloid complex, hippocampus, midbrain, and cingulate cortex, that may be related to the complex mechanism of reproduction.

Gn-RH is secreted in a pulsatile fashion, which results in the pulsatile secretion of gonadotropins from the anterior pituitary. An increase in the pulsatile release of Gn-RH is essential for the onset of puberty [33]. Gn-RH secretion and Gn-RH mRNA expression are influenced by estrogen, progesterone, and some neurotransmitters, such as GABA, NPY, opioids, glutamate, and noradrenaline [31, 33]. Estrogen and progesterone increase Gn-RH mRNA in the hypothalamus of rats. GABA reduces Gn-RH mRNA expression levels and its release.

Recently, kisspeptins have been identified to be novel key regulators for Gn-RH [21, 22]. The kisspeptins are the peptide products of the KiSS-1 gene and the endogenous agonists for the GPR54 receptor. Although KiSS-1 was initially discovered as a metastasis suppressor gene, the kisspeptin/GPR54 system has been shown to be a key regulator of the reproductive system. Disrupted GPR54 signaling causes hypogonadotropic hypogonadism [34]. An activating mutation in the GPR-54 gene resulted in central precocious
puberty [35]. Central or peripheral administration of kisspeptin potently stimulates the hypothalamic-pituitary-gonadal axis, and increases circulating gonadotrophin concentrations in a number of animal models. These effects appear likely to be mediated via the stimulation of the hypothalamic gonadotrophin-releasing hormone system, although kisspeptins may have direct effects on the anterior pituitary gland. Moreover, hypothalamic KiSS-1 gene expression is regulated by circulating sex steroids.

2.3.4 Thyrotropin-Releasing Hormone (TRH)

TRH is a first-discovered hypothalamic hormone consisting of three amino acids (pGlu-His-Pro-NH$_2$) [4, 5]. TRH is the shortest peptide among the hypothalamic hormones. TRH stimulates the secretion of both TSH and prolactin from the anterior pituitary lobe. TRH-containing neurons are found in the paraventricular nucleus, perifornical area, periventricular nucleus, lateral hypothalamus, and hypothalamus. TRH is present not only in the hypothalamus but also in the other regions of the brain, and may act as a neurotransmitter or neuromodulator. TRH increases locomotor activity, increases body temperature, causes trembling behavior, and decreases food intake, etc. [19].

2.3.5 Hypothalamic Control on the Prolactin Secretion

Prolactin release from the pituitary lactotropes is regulated by a tonic inhibitory control of dopamine derived from the hypothalamus [36]. The lesions in hypothalamus or pituitary stalk result in the decreased delivery of hypothalamic hormones to the anterior pituitary gland, and cause hypofunction of anterior pituitary hormones, except for prolactin. Prolactin secretion is rather increased in the lesions of hypothalamus or pituitary stalk because of decreased delivery of dopamine to the anterior pituitary.

Several candidates for prolactin-releasing factor (PRF) have been proposed; these include TRH, VIP [37], peptide histidine methionine (PHM), galanin, oxytocin, and prolactin-releasing peptide (PrRP) [38]. Although all these peptides have a prolactin-releasing activity, a physiological PRF has not been identified. VIP is a potent vasodilator peptide consisting of 28 amino acids, which is abundant in the gastrointestinal tract and the brain. The VIP precursor generates another bioactive peptide called PHM (peptide histidine isoleucine (PHI) in porcine and rat) by post-translational proteolytic processing [39]. PHM has a structural similarity to VIP and similar biological actions such as vasodilator action and prolactin-releasing activity.

2.3.6 Receptors for the Hypothalamic Hormones and Their Mutations

Receptors for hypothalamic hormones: CRH, GH-RH, somatostatin, TRH, and Gn-RH, belong to the GTP-binding protein (G protein) coupled receptor superfamily. They have a common structure with seven transmembrane domains. Receptors for each peptide consist of several subtypes, which have different pharmacological properties. For example, there are at least five somatostatin receptor subtypes: SSTR1, SSTR2, SSTR3, SSTR4, and SSTR5. SSTR5 is a receptor subtype which is predominantly expressed in the pituitary.

CRH receptors consist of two subtypes: CRH receptor type 1 and 2. CRH receptor type 1 is further divided into CRH receptor type 1a, 1b, 1c, 1d, 1e, 1f, 1g, and 1h. CRH receptor type 2 is also divided into CRH receptor type 2α, 2β, and 2γ. Both CRH receptor type 1 and type 2 are expressed in various organs including the brain. Particularly, CRH receptor type 1 is expressed in the anterior pituitary lobe and mediates the CRH effect on ACTH release. CRH receptor type 2 is widely expressed in various organs, including brain and heart, and may be important in the regulation of the recovery phase of the stress response. CRH receptor type 2 mediates the countershock responses, such as hypotensive, cardioprotective, anxiolytic, and anorexic responses. CRH and urocortin, a CRH family peptide consisting of 40 amino acids, act on both CRH receptor type 1 and 2. On the other hand, two newly identified CRH family peptides, stresscopin (urocortin III) and stresscopin-related peptide (urocortin II) are specific ligands for CRH receptor type 2 [23–25].

Some mutations in the genes coding these receptors for hypothalamic hormones result in hypopituitary function. There have been several case reports on hypogonadotropic hypogonadism [40, 41], short stature (dwarfism) [42–44], or central hypothyroidism [45], which were caused by the mutations in the Gn-RH receptor, the GH-RH receptor or the TRH receptor, respectively (Table 2.2).

The signals from the hypothalamic hormone receptors are transmitted by the G proteins to the second messengers. For example, GH-RH uses cAMP as a second messenger to

<table>
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<tr>
<th>Hypothalamic hormones</th>
<th>Symptoms &amp; signs</th>
<th>Refs</th>
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<tbody>
<tr>
<td>Gn-RH</td>
<td>Hypogonadotropic hypogonadism</td>
<td>[40, 41]</td>
</tr>
<tr>
<td>GH-RH</td>
<td>Short stature (dwarfism)</td>
<td>[42–44]</td>
</tr>
<tr>
<td>TRH</td>
<td>Central hypothyroidism</td>
<td>[45]</td>
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stimulate GH secretion and proliferation of normal pituitary somatotrophs. The signal of GH-RH is transmitted from the GH-RH receptors to the G protein. The G proteins involved in the signal transduction are heterodimers consisting of α, β, and γ subunits. Activity of adenyl cyclase is regulated by at least two G proteins; Gs is responsible for the stimulation of catalytic activity, whereas Gi mediates the inhibition of this enzyme. Mutations that lead to constitutive activation of \( G_{s}\) have been identified in a subset of human GH-secreting pituitary tumors [46, 47].

The McCune Albright syndrome is a sporadic disease characterized by cutaneous hyperpigmentation, polyostotic fibrous dysplasia, and multiple endocrinopathies, including precocious puberty, hyperthyroidism, hypercortisolism, GH-secreting pituitary adenoma, and hyperprolactinemia. The McCune Albright syndrome is caused by the mutations in the gene encoding \( G_{s}\) protein, that lead to constitutive activation of \( G_{s}\) and increased cAMP formation [48, 49]. These diverse metabolic abnormalities actually share the involvement of cells that respond to extracellular signals through activation of the hormone-sensitive adenyl cyclase system. Only GH-secreting pituitary tumors and not other types of pituitary tumors have been described in patients with McCune Albright syndrome, although somatic mutations of Gs may occur in all pituitary cell lines. This may be caused because only the somatotrophs respond with uncontrolled proliferation [48].

### 2.3.7 Hypothalamic Hormone-Secreting Tumors

Hypothalamic hormone-secreting tumors arise mostly from the peripheral tissues. There are a limited number of case reports on hypothalamic hormone-secreting tumors in the hypothalamus or in the area near the hypothalamus. For example, hypothalamic hamartoma secreting Gn-RH is one of the causes of precocious puberty [40]. There are case reports on intrasellar or hypothalamic gangliocytoma secreting CRH or GH-RH [50, 51]. The majority of hypothalamic hormone-secreting tumors arise from the peripheral tissues belonging to the APUD system, such as the lung (carcinoid tumor), thymus (thymoma), pancreatic islet, adrenal medulla (pheochromocytoma), and sympathetic ganglia (neuroblastoma and ganglioneuroblastoma), but many ectopic hormones are also secreted by apparently non-APUD cells [52].

#### 2.3.7.1 Gn-RH-Secreting Hypothalamic Hamartoma

Hamartoma of the central nervous system is a congenital malformation characterized as heterotrophic and hyperplastic tissue that is usually encountered at the base of the brain, the interpeduncular cistern, or within the hypothalamus, and located in proximity to the tuber cinereum and the mammillary bodies [53, 54]. Hypothalamic hamartomas are often associated with precocious puberty. Thirty-seven (74%) of the 50 tissue-proved cases of hamartomas found in the literature showed precocious puberty [54]. Mechanisms underlying this association remain to be determined. One possibility is that the pressure applied by the tumor directly to the hypothalamic centers causes abnormal function. Neuronal stimulation via myelinated fibers connecting the hamartoma to the hypothalamus has also been proposed. Another possibility is that neurons in the aberrant tissue secrete a hormone or hormones that prematurely activate the pituitary-gonadal axis. There are reports of the presence of Gn-RH in the hypothalamic hamartomas obtained from patients with precocious puberty [55, 56].

#### 2.3.7.2 GH-RH-Secreting Tumors

GH-RH-producing tumors with acromegaly arise both from intracranial tissues and extracranial tissues. The association of a gangliocytoma in the hypothalamus with acromegaly has been reported since the 1950s. Intrasellar or hypothalamic gangliocytomas with acromegaly have been shown to secrete GH-RH [52].

GH-RH was originally isolated from the tumor tissue of a pancreatic islet cell tumor in a patient with acromegaly [7, 8], and is produced by various tumors, including islet cell pancreatic tumors, small cell lung carcinomas, bronchial adenocarcinomas, carcinoids, pancreatic adenocarcinomas, breast carcinomas, ovarian carcinomas, pheochromocytomas, medullary thyroid carcinomas, and ganglioneuroblastomas [57]. Although the tumor tissues contain GH-RH, most of the patients with these tumors are free of acromegaly, a symptom which is due to the GH hypersecretion. In only a small number of patients with these tumors, acromegaly occurred clinically [58], possibly because the hypersecretion of GH-RH from the tumor was large enough to cause hypersecretion of GH from the pituitary. The most frequent GH-RH-secreting extracranial tumors with acromegaly are carcinoids (69% of the cases), most often located in the lung (78%) or gastrointestinal tract (11%), followed by islet cell tumors (34%). One cystic bronchial adenoma, one pheochromocytoma and one paraganglioma with acromegaly were also reported [58].

#### 2.3.7.3 CRH-Secreting Tumors

There is one case report of Cushing’s disease associated with an intrasellar gangliocytoma producing CRH [51]. Most CRH-secreting tumors, however, arise from the peripheral tissues. Ectopic CRH secretion is usually accompanied by ectopic ACTH secretion. In other words, CRH is expressed
in the tumor tissues of many of ectopic ACTH-secreting tumors, such as bronchial carcinoids, neuroendocrine tumors of thymus, small cell carcinomas of the lung, colon carcinomas, nephroblastomas, and thyroid medullary carcinomas. In these ectopic ACTH/CRH-secreting tumors, plasma ACTH levels are elevated whereas plasma CRH levels are rarely elevated, suggesting that the tumor CRH is not likely to act on the pituitary, but may affect the ACTH secretion from the tumor as an autocrine/paracrine regulator. Two cases of pure CRH-containing tumors have been reported: metastatic carcinoma of the prostate [59] and thyroid medullary carcinoma [60].

It is well-known that pheochromocytomas express a variety of neuropeptides and vasoactive peptides, such as NPY, VIP, GH-RH, somatostatin, CGRP etc. Pheochromocytomas also express ACTH and CRH [61]; ACTH and CRH are detectable in tumor tissues of most pheochromocytomas by radioimmunoassay. Plasma levels of ACTH and CRH are, however, not elevated in most cases of pheochromocytomas that are therefore free from Cushing syndrome. A very limited number of patients with pheochromocytomas show the hormone excess syndromes, such as Cushing syndrome [62].

2.3.7.4 Somatostatin-Secreting Tumors (Somatostatinomas)

Main symptoms and signs of somastostatinoma are insulin-sensitive, nonketosis-prone diabetes, steatorrhea, and cholelithiasis. About 47% of somatostatinomas arise in the pancreatic islets [63]. Somatostatin overproduction was also found in the carcinoid tumors arising in the small intestine, medullary thyroid carcinomas, pheochromocytomas, small cell carcinomas of the lung, and retinoblastomas. The incidence of somatostatinoma syndrome is, however, not so high (18.5% in pancreatic somatostatinomas and 2.5% in extra-pancreatic somatostatinomas). About half cases of somastostatinomas are malignant.

2.4 Development of Hypothalamus and Transcriptional Factors

Recent studies in gene knockout mice have revealed that certain transcriptional factors are essential for the development of the hypothalamic magnocellular and parvocellular neurosecretory system. These transcriptional factors include Brain-2 (Brn-2), Sim1, Orthopedia (Otp), Arnt2, and Gsh-1.

Brn-2 belongs to the class III POU gene family [64, 65]. The POU domain is a conserved DNA-binding motif, which is about 150 amino acid residues long and consists of two highly conserved regions separated by a 15 to 20 amino acid residue linker region. Brn-2 is expressed in specific regions of the mouse brain including the paraventricular nuclei of the hypothalamus, and binds to and activates the CRH gene promoter. In homozygous Brn-2 mutant embryos, migratory precursor cells for neurons of the paraventricular nuclei and the supraoptic nuclei of the hypothalamus die at E 12.5. All homozygous mutants suffered mortality within 10 days after birth, possibly because of the defect in the secretion of CRH and vasopressin. In heterozygous mice, which had no developmental or histological abnormalities, the expression levels of vasopressin and oxytocin in the hypothalamus were half those of wild mice. Thus, Brn-2 is essential for the development of the magnocellular and parvocellular neurons of the paraventricular nucleus and supraoptic nucleus, which secrete CRH, vasopressin, and oxytocin.

Sim1 and Arnt2 are members of basic Helix-Loop-Helix (bHLH)-PAS (a conserved sequence among Per, AhR/Arnt and Sim) family of transcription factors [66, 67]. These transcription factors are mainly classified into two groups: the AhR (Arylhydrocarbon receptor) group and Arnt (AhR nuclear translocator) group. The AhR group, which includes Sim1, does not dimerize with themselves or other members within the group, but they do heterodimerize with members of the Arnt group. Sim1 is expressed in the paraventricular, anterior periventricular, and supraoptic nuclei during the development of the hypothalamic-pituitary axis. The expression of Arnt2 is limited to the neural tissue, whereas Arnt is broadly expressed in various tissues. Sim1−/− mice and Arnt2−/− mice show similar phenotypes. They die shortly after birth. The supraoptic nuclei and paraventricular nuclei are hypocellular in both types of mice. At least five distinct types of secretory neurons, which secrete oxytocin, vasopressin, TRH, CRH, and somatostatin, respectively, are absent in the paraventricular, anterior periventricular, and supraoptic nuclei of Sim1−/− mice. Similarly, in the mutant Arnt2 mice, secretory neurons of oxytocin, vasopressin, CRH, and somatostatin are completely absent in the supraoptic and paraventricular nuclei. During the development of the Sim1 mutant or Arnt2 mutant hypothalamus, the prospective paraventricular/supraoptic region fails to express Brn-2, suggesting that Sim1 and Arnt2 function upstream to maintain Brn-2 expression.

Otp is a highly conserved homeodomain-containing factor that is expressed during embryonic development in neurons giving rise to the paraventricular, supraoptic, anterior periventricular, and arcuate nuclei of hypothalamus [68]. In homozygous Otp−/− mice, paraventricular, supraoptic and anterior periventricular nuclei were absent, whereas arcuate nucleus was impaired, but present. Otp−/− mice failed to express CRH, TRH, vasopressin, oxytocin, and somatostatin, and die soon after birth. They retained a normal expression of GH-RH in the arcuate nucleus.
of these transcriptional factors.

abnormal hypothalamo-pituitary functions due to mutations in the other hand, there have been no reports on human cases of these transcriptional factors and hypothalamic hormones. On the other hand, there have been no reports on human cases of abnormal hypothalamo-pituitary functions due to mutations in the transcriptional factors of neurohypophysis.

Gsh-1 is a homeobox gene that is essential for GH-RH gene expression in the arcuate nucleus [69]. Gsh-1−/− mice exhibit extreme dwarfism, sexual infantilism, and significant perinatal mortality, with small-sized and hypocellular pituitary.

Figure 2.7 shows summary of the relationship between these transcriptional factors and hypothalamic hormones. On the other hand, there have been no reports on human cases of abnormal hypothalamo-pituitary functions due to mutations of these transcriptional factors.

2.5 Neurohypophysis

The human neurohypophysis is described as consisting of three parts: (1) the median eminence of the hypothalamic tubercinereum; (2) the infundibular stem, which constitutes the pituitary or hypothalamic stalk, together with the portion of adenohypophysis surrounding it (part tuberalis); and (3) the pars nervosa (posterior neural lobe) or infundibular process [70].

Vasopressin and oxytocin are produced in the magnocellular neurons of the paraventricular and supraoptic nuclei, transported by the axonal transport to the posterior pituitary lobe (posterior neural lobe), and released there into circulation (Fig. 2.2). The posterior pituitary lobe consists mainly of nerve fibers of the hypothalamic neurons, pituicytes which are thought to be supportive cells (a kind of glial cells) and the vascular tissues. Anterior pituitary cells, mostly ACTH cells, invade into and are scattered in the posterior pituitary lobe.

Vasopressin is also called anti-diuretic hormone (ADH) following its main actions on the kidney. In humans, rats and mice, vasopressin has an arginine residue at the position 8, and is therefore called arginine vasopressin, while lysine vasopressin found in pigs has a lysine residue at the position 8. The schematic structures of precursors of vasopressin (arginine vasopressin) and oxytocin are shown in Fig. 2.8. The cDNAs encoding the precursors of oxytocin and vasopressin code other proteins, neurophysin I and neurophysin II, respectively. Neurophysins are generated by proteolytic processing of the precursors in secretory granules, and are supposed to have important roles in the axonal transport of oxytocin and vasopressin from the hypothalamus to the neurohypophysis.

The most important factors that regulate the production and the secretion of vasopressin are plasma osmolarity and circulating blood volume. Increases in plasma osmolarity, or decreases in circulating blood volume, such as hemorrhagic shock, stimulate the release of vasopressin from the neurohypophysis and elevate plasma levels of vasopressin. Several neurotransmitters and neuropeptides, such as angiotensin II, natriuretic peptides and endorphin, regulate the production and secretion of vasopressin in the hypothalamus and the neurohypophysis. Acetylcholine stimulates vasopressin secretion, whereas beta-adrenergic agonists inhibit the vasopressin secretion. Angiotensin II and endorphin release vasopressin, while natriuretic peptides inhibit its secretion. Vasopressin actions are mediated by tissue-specific G protein-coupled receptors, which are currently classified into V1 vascular (vasoconstrictor action), V2 renal (anti-diuretic action), and V3 pituitary (or V1b) (stimulation of ACTH release) subtypes [17, 18, 71], as described in the previous section. 2.2 Physiology and anatomy of the hypothalamus.

The secretion of oxytocin is stimulated by the so-called “milk let-down reflex.” The stimulus of suckling causes a neurogenic reflex that is transmitted from afferent nerve endings in the nipple to the hypothalamus, where the secretion of oxytocin is stimulated. Oxytocin causes contraction of the myoepithelial cells in the breast and stimulates the secretion of milk. Furthermore, oxytocin has uterine-contracting actions. These actions are mediated by the oxytocin-specific G-protein coupled receptor. Physiological significance of oxytocin in men and non-pregnant women remains to be determined.

Recent studies have shown that mice lacking oxytocin or oxytocin receptor are both viable and fertile [72, 73]. Oxytocin-deficient female mice, however, had the inability to nurse in spite of normal maternal behavior, and therefore offspring die shortly after birth [72]. Moreover, female mice lacking oxytocin receptor exhibited normal parturition, but demonstrated defects in lactation and maternal nurturing [73]. Adult male mice lacking oxytocin receptor showed deficits in social discrimination and elevated aggressive behavior. Oxytocin may therefore have a neurotransmitter role in the several aspects of social behavior. The defect in oxytocin or oxytocin receptor may be related to elevated
aggressive behavior in certain psychiatric disorders. Furthermore, there has been reports which show that oxytocin is involved in endocrine and neuroendocrine regulation through receptor mediated actions exerted on the brain, heart, vasculature, and kidneys [74–77]. For example, oxytocin receptor is expressed in the heart, and oxytocin has negative and chronotropic effects on cardiac atrium.

2.6 Overview of Diseases of the Hypothalamus and Neurohypophysis

Diseases of the hypothalamus comprise tumors, inflammatory and infectious diseases, and genetic disorders. Tumors found in the hypothalamus include craniopharyngioma, germinoma, teratoma, meningioma, glioma (Fig. 2.9), etc. Some rare tumors that secrete hypothalamic hormones and much more rare cases of hypothalamic hormone receptor mutations are described in the previous sections. Inflammatory diseases include sarcoidosis, histiocytosis, infundibuloneurohypophysitis etc. Infectious diseases such as meningitis (tuberculous, bacterial, viral or fungal) were also found in the hypothalamus and neurohypophysis.

Hypothalamic diseases cause a variety of symptoms and signs, depending on the site of the lesion. These include sexual abnormalities (hypogonadism or precocious puberty), abnormalities in water-electrolyte metabolism (diabetes insipidus, hypernatremia or hyponatremia), hypofunction of anterior pituitary, psychic disturbance, abnormalities in appetite (hyperphagia and obesity, or anorexia), emaciation, thermodyresregulation, sleep disorders (e.g., narcolepsy), and sphincter disturbances. Diseases related to diabetes insipidus, hypogonadism, obesity and abnormal appetite, and the sleep disorder (narcolepsy) are described in later sections. Destructive lesions of the pituitary stalk cause diabetes insipidus and hypofunction of anterior pituitary except for prolactin. These include rupture after head injury, surgical transection, tumor, and granuloma. Diabetes insipidus develops, depending on the level at which the stalk has been sectioned. If the stalk is cut at the level close to the hypothalamus,
Hypothalamus and Neurohypophysis

2.7 Diseases Due to the Dysfunction in Vasopressin Secretion

2.7.1 Diabetes Insipidus

Diabetes insipidus is a disease characterized by polydipsia and polyuria. Diabetes insipidus is caused by deficient production of vasopressin in the hypothalamus (neurogenic or central diabetes insipidus) or the deficient action of vasopressin in the renal tubular cells (nephrogenic diabetes insipidus).

2.7.1.1 Central Diabetes Insipidus

Central diabetes insipidus is classified into three categories, familial, secondary, and idiopathic, according to the causes (Table 2.3). Familial diabetes insipidus is a very rare disorder and is characterized by autosomal dominant inheritance. Secondary diabetes insipidus is caused by tumors, infection, inflammatory diseases, infiltrative processes and trauma that damage the hypothalamic-neurohypophysial system. Tumors and inflammatory diseases in the hypothalamus and neurohypophysis are described in the following sections.

Table 2.3 Classification of central (neurogenic) diabetes insipidus.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Familial diabetes insipidus</strong></td>
<td></td>
</tr>
<tr>
<td>Autosomal dominant</td>
<td></td>
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<tr>
<td>Wolfram syndrome</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary diabetes insipidus</strong></td>
<td></td>
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<tr>
<td>Tumors</td>
<td></td>
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<tr>
<td>Primary tumors (craniopharyngioma, suprasellar germinoma, glioma etc.)</td>
<td></td>
</tr>
<tr>
<td>Metastatic carcinomas (lung, breast, leukemia, lymphoma etc.)</td>
<td></td>
</tr>
<tr>
<td>Anterior pituitary tumors (mostly, postoperative)</td>
<td></td>
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<tr>
<td>Infection (tuberculosis, AIDS-associated infection etc.)</td>
<td></td>
</tr>
<tr>
<td>Granulomatous diseases (sarcoidosis, Langerhans'-cell histiocytosis, non-Langerhans'-cell histiocytosis, etc.)</td>
<td></td>
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<tr>
<td>Lymphocytic adenohypophysitis</td>
<td></td>
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<tr>
<td>Lymphocytic infundibuloneurohypophysitis</td>
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<tr>
<td>Guillain-Barré syndrome</td>
<td></td>
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<tr>
<td>Aneurysms</td>
<td></td>
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<tr>
<td>Infiltrative processes (hemochromatosis, amyloidosis)</td>
<td></td>
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<tr>
<td>Trauma</td>
<td></td>
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<tr>
<td><strong>Idiopathic diabetes insipidus (Lymphocytic infundibuloneurohypophysitis)</strong></td>
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</table>

Autosomal Dominant Familial Diabetes Insipidus

Missense mutations of the vasopressin-neurophysin II gene have been identified in some families with familial diabetes insipidus. A single base substitution was reported in one of the two alleles of the vasopressin-neurophysin II gene in families with familial diabetes insipidus [78, 79]. These mutations result in one-amino acid substitution in the neurophysin II moiety (Ser to Gly at amino acid position 57 in the neurophysin II moiety [78]; and Val to Gly at amino acid position 17 in the neurophysin II moiety [79]). Neurophysins bind to their associated peptide hormones, vasopressin and oxytocin, after proteolytic processing of the precursor. The amino acid substitution in neurophysin II may result in its conformational change. Such changes may impair functions of neurophysin II; the protecting action for arginine vasopressin from proteolytic degradation and the assisting action of arginine vasopressin in its axonal transport. Moreover, the mutated neurophysin II may impair the function of normal neurophysin II molecules, possibly by a heterodimer formation.

A mutation was also found in the gene region encoding the vasopressin signal peptide. A point mutation causes a substitution of threonine for alanine at the last amino acid of the signal peptide in these patients [80–82]. The signal peptide directs the precursor protein to enter the endoplasmic reticulum, where the proteolytic cleavage of the precursor occurs. The amino acid change possibly alters the cleavage of the signal peptide and results in inefficient processing. Thus, autosomal dominant central diabetes insipidus is caused by many mechanisms.

The mutant arginine vasopressin-neurophysin II complex may accumulate slowly in the magnocellular neurons and lead to the death of these neurons [83]. Autopsy studies of patients with autosomal dominant diabetes insipidus show a markedly subnormal number of magnocellular neurons and associated moderate gliosis [84, 85].

Wolfram Syndrome

Wolfram syndrome is an autosomal recessive neurodegenerative disorder associated with juvenile-onset non-immune insulin-dependent diabetes mellitus, progressive optic atrophy, sensorineural deafness, and diabetes insipidus, also known as DIDMOAD (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, and Deafness) [86]. Patients present with diabetes mellitus followed by optic atrophy in the first decade, central diabetes insipidus and sensorineural deafness in the second decade, dilated renal outflow tracts early in the third decade, and multiple neurological abnormalities early
in the fourth decade [86]. Central diabetes insipidus occurred in about 73% of the patients [87]. A Wolfram gene (WFS1) has been mapped to chromosome 4p16.1 [88]. The WFS1 encodes an 890 amino acid protein, which is a membrane glycoprotein and localizes in the endoplasmic reticulum [89]. WFS1 is widely expressed in the brain, including hippocampus, amygdaloid, and hypothalamus, consistent with a variety of neurological manifestations and central diabetes insipidus. Although the relationship between the WFS1 deficiency and the hypofunction of hypothalamic vasopressin neurons is not fully clarified, recent studies have shown the relationship between the WFS1 deficiency and pancreatic beta-cell loss [89, 90]. In pancreatic islets of wfs1-deficient mice, WFS1-deficiency increased endoplasmic reticulum stress and caused pancreatic beta-cell loss through impaired cell cycle progression and increased apoptosis [90].

Idiopathic Diabetes Insipidus, Lymphocytic Infundibuloneurohypophysitis, and Lymphocytic Adenohypophysitis

Idiopathic diabetes insipidus comprises approximately 30% of central diabetes insipidus. Lymphocytic infundibuloneurohypophysitis has been proposed as an important cause of what was previously considered to be idiopathic diabetes insipidus by Imura et al. [91]. On the other hand, lymphocytic adenohypophysitis is a rare inflammatory disease which primarily affects adenohypophysis and is probably caused by autoimmunity (Figs. 2.10 and 2.11). Approximately 19% of the patients with lymphocytic adenohypophysitis, however, have diabetes insipidus [92]. Lymphocytic infundibuloneurohypophysitis and lymphocytic adenohypophysitis are described in details in the later section 2.9 “Inflammation in the hypothalamus and neurohypophysis.”

2.7.1.2 Nephrogenic Diabetes Insipidus

Congenital nephrogenic diabetes insipidus is a hereditary disorder characterized by the inability of the kidney to concentrate urine in response to arginine vasopressin. This disease is caused by mutations in the V2 receptor gene (X-linked recessive trait) or the gene of the renal water channel, aquaporin-2 (AQP2) (autosomal recessive trait).

The renal V2 receptor mediates anti-diuresis by activation of adenylate cyclase in the distal parts of the nephron. In most
cases, congenital nephrogenic diabetes insipidus was inherited in an X-linked recessive mode, and caused by mutations in the V2 receptor gene, which is localized to the long arm of the X chromosome. Rosenthal et al. reported a patient of congenital nephrogenic diabetes insipidus who had a deletion in the open reading frame of the V2 receptor gene, causing a frame shift and premature termination of translation in the third intracellular loop of the receptor protein [93].

The activation of the V2 receptor on renal collecting tubules stimulates adenylyl cyclase via the stimulatory G-protein (Gs) and promotes the cAMP-mediated incorporation of AQP into the luminal surface of these cells. There are at least ten members of AQP: AQP0-AQP9. AQP2 is the vasopressin sensitive water channel in renal collecting ducts. Nephrogenic diabetes insipidus with autosomal recessive inheritance is caused by compound heterozygote or homozygosity for mutations in the AQP2 gene [94, 95].

### 2.7.2 SIADH (Syndrome of Inappropriate ADH Secretion)

SIADH is a disorder characterized by hyponatremia and impaired water excretion in the absence of hypovolemia, hypotension, or a deficiency of cardiac, renal, thyroid, or adrenal function. This disorder is caused by continual release of vasopressin in spite of a subnormal plasma osmolarity. The diseases most often associated with SIADH are shown in Table 2.4. The most common causes for SIADH are malignant diseases, especially small cell or oat cell carcinomas of the lung [96], which produce and secrete vasopressin. The other malignant tumors associated with SIADH include carcinomas of the pancreas, duodenum, bladder and prostate, thymomas, lymphomas, and Ewing’s sarcomas. Non-malignant pulmonary diseases are associated with SIADH, probably because hypoxia, hypercapnea or increased intrathoracic pressure may stimulate the release of vasopressin. The lesions in the brain as shown in Table 2.4 may directly or indirectly stimulate the hypothalamic-neurohypophysis to secrete vasopressin. Several drugs to stimulate the vasopressin release are also known.

### 2.7.3 Essential Hypernatremia (Central Hypernatremia or Hypothalamic Hypernatremia)

The association of hypernatremia with neurologic lesions has been known for a long time. Particularly, lesions of the hypothalamus are likely to lead to the development of sustained hypernatremia and hyperosmolality as a consequence of specific disturbances in the neuroendocrine regulation of osmolality. In 1962, Welt suggested the use of the term “essential hypernatremia” to describe such patients [97]. The clinical features characteristic of the syndrome “essential hypernatremia” include: (1) chronic but fluctuating elevations of serum sodium level in the absence of decreased plasma volume; (2) impaired osmotic regulation of vasopressin secretion, although the endogenous production of vasopressin may be partially intact; and (3) hypernatremia which does not respond to chronic fluid overloading, but which may be corrected by vasopressin administration [98–100]. Thus, the sustained hyperosmolality in the patients with essential hypernatremia is the result of an elevated osmotic threshold for release of vasopressin. As essential hypernatremia is caused by abnormalities in the control of the brain over the water-electrolyte metabolism, “central hypernatremia” or “hypothalamic hypernatremia” might be a more appropriate nomenclature for this disorder rather than “essential hypernatremia.”

### 2.8 Tumors and Cystic Lesions in the Hypothalamus and Neurohypophysis

Various types of tumors and cystic lesions affect the hypothalamus and sellar region. The tumors include gliomas (Fig. 2.9), meningiomas, gangliocytomas, hamartomas, craniopharyngiomas, germinomas, teratomas etc. Hypothalamic hormone-secreting gangliocytomas and hamartomas are described in the earlier section, 2.3.7 “Hypothalamic hormone-secreting tumors.” In this section, other tumors and cystic lesions that specifically affect the hypothalamus are discussed. Rathke’s cleft cyst arises mainly intrasellarly, and often suprasellarly, and therefore is also described here.
2.8.1 Craniopharyngioma

Craniopharyngioma is a cystic neoplasm derived from the remnants of Rathke’s pouch (Fig. 2.12). It originates from the pituitary stalk and is usually suprasellar. Craniopharyngioma can be clinically aggressive with finger-like infiltration to the surrounding structures, even if it is histologically benign. Craniopharyngioma may be seen at most ages, but it is most frequently diagnosed in childhood. It is the most common neoplasm associated with hypothalamo-pituitary dysfunction. Its clinical manifestations include visual dysfunction, anterior pituitary dysfunction, growth retardation, sexual dysfunction, diabetes insipidus and cranial nerve abnormalities. Histologically, it is formed by complex cords or islands of squamous cells, and the outer layers of cells are usually cuboid to cylindrical. Craniopharyngioma has a cystic structure which is formed by the lining stratified squamous epithelium. Areas of mineralization or ossification are often found in the tumor tissue (Fig. 2.12). Calcification can be found on X-ray examination in the sellar or suprasellar region.

2.8.2 Rathke’s Cleft Cyst

Rathke’s cleft cyst is a non-neoplastic, developmental sellar and/or suprasellar cystic lesion lined by a single layer of ciliated cuboidal or columnar epithelium (Figs. 2.13 and 2.14). It derives from a remnant of Rathke’s pouch. Rathke’s cleft cyst rarely comes symptomatic. When its size is enlarged by the accumulation of colloid secretion (more than 1 cm in diameter), symptoms and signs due to the compression by the cyst appear. These include hypopituitarism,

Fig. 2.12 Craniopharyngioma (H & E). Bar = 50 µm (Courtesy of Dr. H. Ikeda, Department of Neurosurgery, Southern Tohoku General Hospital, Koriyama, Japan.)

Fig. 2.13 Cyst wall of Rathke’s cleft cyst (H & E). Bar=50 µm (Courtesy of Dr. H. Ikeda, Department of Neurosurgery, Southern Tohoku General Hospital, Koriyama, Japan.)
hyperprolactinemia, diabetes insipidus, headache, and impairment of visual acuity and visual field defects [101]. A case of Rathke’s cleft cyst with SIADH is also reported [102]. Approximately 50% of Rathke’s cleft cysts are intrasellar, and the others are suprasellar, or suprasellar and intrasellar [103].

2.8.3 Germ Cell Tumors

Germ cell tumors include germinomas, choriocarcinomas, yolk sac tumors, embryonal carcinomas, teratomas with various degree of differentiation and mixed germ cell tumors. These tumors are presumed to originate from embryonic nests of germ cells, and found in the gonads and extragonadally in the midline structures of the body. In the central nervous system, germ cell tumors arise in the pineal region and in the hypothalamohypophyseal region. Among the germ cell tumors arising in the hypothalamohypophyseal region, germinomas are the most common (suprasellar germinoma) [104]. Approximately 20% of germinomas produce human chorionic gonadotropin [105]. Clinical manifestations of suprasellar germinomas are diabetes insipidus, visual disturbance, and hypopituitarism (growth retardation or hypogonadism). Bacterial, viral, fungal or tuberculous etc.) can affect the hypothalamus and neurohypophysis. While tuberculosis was the most common among the infectious diseases of the endocrine organs, opportunistic infections involving the endocrine organs in patients with acquired immunodeficiency syndrome (AIDS) have been increasingly recognized [106]. A case of central diabetes insipidus due to cytomegalovirus infection of the hypothalamus with AIDS has been reported [107].

Hypophysitis is an inflammatory lesion of the pituitary gland, and usually classified as adenohypophysitis and infundibuloneurohypophysitis depending on the location of the main lesion in the pituitary gland. Adenohypophysitis clinically and radiologically mimics tumors of the sellar region, causing mass effects such as headache and visual impairment. Adenohypophysitis primarily affects the anterior pituitary lobe, but may result in hypophyseal and/or hypothalamic dysfunction such as diabetes insipidus from inflammatory destruction of the hypophysis (panhypophysitis) or compression of the residual normal gland by edema. Whereas secondary hypophysitis caused by infection or systemic disease is relatively rare today, primary (idiopathic, or probably autoimmune) hypophysitis is currently the most common form of pituitary inflammation. Primary hypophysitis include three histopathological conditions: lymphocytic hypophysitis, granulomatous hypophysitis, and xanthomatous hypophysitis [108].

2.9 Inflammation in the Hypothalamus and Neurohypophysis

Inflammatory diseases (e.g., Langerhans’-cell histiocytosis, Erdheim-Chester disease, sarcoidosis, and lymphocytic infundibuloneurohypophysitis), and infectious diseases (e.g., Langerhans’-cell histiocytosis is a granulomatous disease that occurs mostly in children between 1 and 4 years of age [109, 110]. This disorder is characterized by the proliferation...
and infiltration of abnormal histiocytes within various tissues, which are morphologically and immunologically similar to Langerhans’ cells, leading to the name Langerhans’-cell histiocytosis. Chronic recurrent Langerhans’-cell histiocytosis (Hand-Schuller-Christian disease) typically involves a triad of diabetes insipidus, proptosis, and destructive bone lesions, whereas the acute disseminated form of Langerhans’-cell histiocytosis (Letterer-Siwe disease) is characterized by hepatosplenomegaly, fever, thrombocytopenia, anemia, and a rash. Eosinophilic granuloma is characterized by solitary bony disease. The key diagnostic feature of this disorder is the presence of abnormal aggregates of Langerhans’ cells. These cells, unlike other histiocytes, are characterized by immunohistochemical positivity for CD1a and S-100 protein and by the ultrastructural presence of membranous cytoplasmic structures, 200–400 nm in width and shaped like tennis rackets, that are known as Birbeck granules [111, 112].

Diabetes insipidus and growth retardation are the prominent endocrine manifestations of Langerhans’-cell histiocytosis [112, 113]. Galactorrhea, hypogonadism, and panhypopituitarism are rarely associated with this disorder. Histiocytic infiltration results in a hypothalamic dysfunction with a secondary partial or complete hypopituitarism. This hypopituitarism is due to deficient trophic stimulation or inhibition by hypothalamic hormones or dopamine.

### 2.9.2 Non-Langerhans’-Cell Histiocytosis (Erdheim-Chester Disease)

Erdheim-Chester disease is an idiopathic progressive non-Langerhans’-cell histiocytosis characterized by xanthogranulomatous infiltration of foamy macrophages [114–116]. This rare disorder (only about 500 cases in the literature) is typically manifested as pain and sclerotic lesions in the long bones, particularly the diaphyses, but extraskeletal involvement is common. The common sites involved are the orbit, the hypothalamo-pituitary-sella area, the retroperitoneal and periaortic tissues, the lungs and the heart. Infiltration to the pituitary stalk sometimes causes diabetes insipidus [115, 116].

### 2.9.3 Sarcoidosis

The hypothalamus and pituitary is the most commonly affected regions by sarcoidosis although endocrine manifestation is relatively rare in sarcoidosis [117–119]. The central nervous system is involved in about 5% of all cases of sarcoidosis and diabetes insipidus occurs in 33% patients with neurosarcoidosis [120]. In addition to diabetes insipidus, patients with sarcoidosis often exhibit hypothalamic disturbances and anterior pituitary hormone deficiency [117–119]. Histologically, sarcoidosis shows noncaseous granulomatous tissue with multinucleated giant cells of foreign body type.

#### 2.9.4 Lymphocytic Infundibuloneurohypophysitis and Lymphocytic Adenohypophysitis

Lymphocytic infundibuloneurohypophysitis was proposed to be one major cause of what was previously considered to be idiopathic diabetes insipidus by Imura et al. [91]. They studied 17 patients with idiopathic diabetes insipidus. Magnetic resonance imaging (MRI) showed that nine of the 17 patients had thickening of the pituitary stalk, enlargement of the neurohypophysis, or both and lacked the hyperintense signal of the normal neurohypophysis. In the remaining eight patients, the pituitary stalk and the neurohypophysis were normal, although the hyperintense signal was absent. The abnormalities of thickening and enlargement were seen on MRI only in the patients who had diabetes insipidus for less than 2 years, and the abnormalities disappeared during follow-up, suggesting that the natural course of the disorder is self-limited. In addition to vasopressin deficiency, two patients had mild hyperprolactinemia and nine had impaired secretory responses of growth hormone to insulin-induced hypoglycemia. The biopsies in two cases revealed chronic inflammation, with infiltration of lymphocytes (mainly T lymphocytes) and plasma cells.

Autoimmune central diabetes insipidus is diagnosed based on the presence of autoantibodies to arginine vasopressin-secreting cells or the coexistence of other autoimmune polyendocrine syndromes. Vasopressin-cell antibodies have been detected with a high incidence (15 out of 22 cases) among patients with complete autoimmune central diabetes insipidus [121]. Pituitary stalk thickening on MRI which suggested lymphocytic infundibuloneurohypophysitis occurred only in patients with positive vasopressin-cell antibodies [121].

Lymphocytic adenohypophysitis is a rare inflammatory disease which primarily affects adenohypophysis and is probably caused by autoimmunity (Figs. 2.10 and 2.11). Approximately 19% of the patients with lymphocytic adenohypophysitis, however, have diabetes insipidus [92, 122]. It predominantly affects women of menstrual age, in particular during late pregnancy or in the postpartum period. More than 70% of patients with this disease are female. Clinically, lymphocytic adenohypophysitis has an acute onset. Clinical
manifestations are headaches, visual symptoms and signs, hypopituitarism and radiological appearance of sellar mass lesion which mimics pituitary adenoma (Fig. 2.10). Lymphoplasmacytic infiltrate is a histological feature of this disease with occasional infiltrate of neutrophils, eosinophils, and macrophages in the anterior pituitary gland (Fig. 2.11). The inflammatory infiltrate was shown in the neurohypophysis of some patients with lymphocytic adenohypophysitis and diabetes insipidus.

### 2.9.5 Other Autoimmune Diseases

Systemic autoimmune diseases, such as giant-cell arteritis [123] and Wegener’s granulomatosis, affect the hypothalamus, the hypophysis and/or the meninges around the sella turcica. In addition, lymphocytic adenohypophysitis and lymphocytic infundibuloneurohypophysitis are frequently associated with autoimmune diseases, such as systemic lupus erythematosus [124]. Circulating anti-pituitary antibodies were detected at higher frequencies in patients with autoimmune thyroid disorders (Hashimoto’s thyroiditis, 13%; Graves’ disease, 7.1%) than in control subjects (0.9%), suggesting that autoimmune hypophysitis is likely to be much more common than previously thought [125, 126]. Thirty-six out of 110 subjects with positive circulating anti-pituitary antibodies had mild or severe GH deficiency and one had central diabetes insipidus [125].

### 2.10 Differential Diagnosis of Mass Lesions That Primarily Involve the Posterior Pituitary

Mass lesions that primarily involve the posterior pituitary are extremely uncommon. The differential diagnoses of neurohypophyseal masses include neoplastic, infiltrative or granulomatous diseases. Primary neoplasms originating from the posterior lobe are extremely rare; the most common are granular cell tumors (choristomas or pituicytomas) [127]. The majority of such tumors remains asymptomatic and is found incidentally at autopsy. Secondary carcinomas involve the posterior pituitary more commonly than the anterior pituitary, and are usually found incidentally at autopsy in cases of disseminated carcinomatosis.

Infiltrative and granulomatous diseases are noted to have a predilection for the posterior pituitary. These include Langerhan’s histiocytosis, sarcoidosis, tuberculosis, and syphilis, which can infiltrate the posterior lobe or pituitary stalk to cause diabetes insipidus [128].

### 2.11 Hypogonadotropic Hypogonadism and Kallmann’s Syndrome

Hypogonadotropic hypogonadism is characterized by failed gonadal function secondary to deficient LH/FSH secretion [129]. Hypogonadotropic hypogonadism is caused by dysfunction of gonadotropic cells due to pituitary lesions, such as tumors, inflammatory diseases, and infiltrative processes (e.g., iron deposition by hemochromatosis) [130], or Gn-RH deficiency in the hypothalamo-pituitary axis. Idiopathic hypogonadotropic hypogonadism is a congenital disorder characterized by Gn-RH deficiency, classically presents with delayed or absent puberty and has a prevalence of about 0.025% in males and about 0.01% in females. About 50% of cases of idiopathic hypogonadotropic hypogonadism are accompanied with congenital anosmia and constitute Kallmann’s syndrome. We describe here hypogonadotropic hypogonadism caused by abnormalities in the hypothalamus.

#### 2.11.1 Kallmann’s Syndrome

Kallmann’s syndrome is characterized by the association of hypogonadism and inability to smell (anosmia). This syndrome is caused by a defect in the migration of olfactory neurons and neurons producing hypothalamic Gn-RH. Fetal Gn-RH neurosecretory neurons fail to migrate from the olfactory placode to the medial basal hypothalamus. The fetal Gn-RH-containing cells and neurites are arrested in their migration to the brain, and end in a tangle around the cribriform plate and in the dural layers adjacent to the meninges beneath the forebrain. Thus, hypogonadotropic hypogonadism is caused by the deficiency of hypothalamic Gn-RH, and the inability to smell is by the absence of olfactory bulbs and tract. This syndrome is genetically heterogenous and can be transmitted as an X-linked, autosomal dominant or autosomal recessive trait.

Loss-of-function mutations in KAL1 and fibroblast growth factor receptor 1 (FGFR1) gene (FGFR1/KAL2) underlie the X-linked form and an autosomal dominant form of the disease, respectively [131, 132]. KAL1 mutations result in a more severe reproductive phenotype than FGFR1/KAL2 mutations [133]. Fibroblast growth factor 8 (FGF8) is a ligand for FGFR1, and loss-of-function mutations in FGF8 underlie both Kallmann’s syndrome and normosmic idiopathic hypogonadotropic hypogonadism [134]. Furthermore, loss-of-function mutations in genes encoding the G protein-coupled prokineticin receptor-2 (PROKR2) and one of its ligands, prokineticin-2 (PROK2) have been shown to underline both Kallmann’s syndrome and normosmic idiopathic hypogonadotropic hypogonadism [135, 136].
The KAL1 gene was located in the critical region on Xp22.3, and encodes anosmin-1, a locally restricted glycoprotein of embryonic extracellular matrices, which has significant similarities with proteins involved in neural cell adhesion and axonal path-finding, and may have a specific role in neuronal migration. There is a functional interaction between anosmin-1 and the FGFR1-FGF2-heparan sulfate complex, leading to amplified responses in the FGFR1 signaling pathway during the nervous system development [137]. The PROK2 signaling system regulates diverse biological processes, including olfactory bulb morphogenesis, and reproduction, through multiple intracellular signaling pathways, including calcium mobilization.

### 2.11.2 Other Hypogonadotropic Hypogonadism Related to the Hypothalamus

In addition to KAL1, FGFR1/KAL2, FGF8, PROKR2, and PROK2, loss-of-function mutations in genes of Gn-RH Receptor (GNRHR)[40, 41], Nasal Embryonic LHRH Factor (NELF)[138], and GPR-54 (kisspeptin receptor) [34, 139] underlie genetic hypogonadotropic hypogonadism due to Gn-RH deficiency. Human cases of Gn-RH deficiency due to the Gn-RH gene mutations have recently been reported [140].

Patients with hypogonadotropic hypogonadism are frequently accompanied by obesity. These include Bardet-Biedl syndrome, Prader Willi syndrome, leptin gene mutation [141, 142], leptin receptor gene mutation [143], and prohormone convertase 1 gene mutation [144, 145]. Frolich syndrome, which is caused by the destruction of ventromedial nucleus of hypothalamus by an invasive tumor, also has both obesity and hypogonadotropic hypogonadism. We describe these diseases in the following section 2.12 Appetite Regulation, Obesity and Anorexia Nervosa. Leptin, not only suppresses the appetite, but also appears to activate the hypothalamo-pituitary gonadal axis. For example, the normal rise of testosterone at onset of puberty in young boys is preceded by a peak of leptin secretion [146]. Moreover, leptin stimulates the secretion of Gn-RH by hypothalamic neurons and gonadotropins by pituitary cells in vitro [147]. Hypogonadotropic hypogonadism is therefore caused by leptin gene mutation [141, 142] or leptin receptor gene mutation [143]. The other diseases with hypogonadotropic hypogonadism and obesity appear to be due to the primary hypothalamic dysfunction. Hypogonadotropic hypogonadism in patients with prohormone convertase 1 gene mutations may arise from impaired processing of hypothalamic hormones including Gn-RH and neuropeptides related to the Gn-RH secretion [145].

### 2.12 Appetite Regulation, Obesity and Anorexia Nervosa

Disruption of the ventromedial hypothalamus produced hyperphagic obesity, while lesions of the lateral hypothalamus caused hypophagia and weight loss. These observations suggest that the existence of ventromedial “satiety” and lateral “feeding” centers. Since the recent discovery of leptin, a peptide hormone derived from adipocytes, studies on the central regulation of appetite and obesity have been greatly advanced.

Leptin is a 167-amino-acid peptide that is secreted from adipocytes; it acts on the brain, particularly the hypothalamus, and suppresses appetite and food intake [12, 148]. Furthermore, leptin stimulates the sympathetic nerve activity and controls the metabolic activity centrally. Leptin was originally described as the product of the mouse obese (ob) gene [12]. In ob/ob mice, obesity was caused by the mutation of the ob gene, which results in a lack of circulating leptin. In contrast, the mutation of the leptin receptor gene causes the obesity in db/db mice. Plasma levels of leptin are elevated in obese subjects, whereas they are low in lean subjects.

A number of neurotransmitters and neuromodulators, mostly neuropeptides, have been demonstrated to regulate the appetite in the hypothalamus (Table 2.5). Leptin secreted by adipocytes is supposed to regulate the appetite by affecting the production and secretion of these neuropeptides in the hypothalamus. Representative appetite-stimulating factors are neuropeptide Y (NPY) (Fig. 2.15.) and the melanin-concentrating hormone (MCH). (Fig. 2.16.).

NPY is a 36 amino acid peptide, originally isolated from porcine brain, and form the pancreatic polypeptide (PP)

#### Table 2.5 Representative neuropeptides, neurotransmitters and hormones that influence eating behavior.

<table>
<thead>
<tr>
<th>Stimulate eating</th>
<th>Inhibit eating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropeptide Y</td>
<td>Leptin&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Melanin-concentrating hormone</td>
<td>α-MSH</td>
</tr>
<tr>
<td>Agouti-related protein</td>
<td>CRH/urocortin</td>
</tr>
<tr>
<td>Orexins (hypocretins)</td>
<td>TRH</td>
</tr>
<tr>
<td>Ghrelin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Cocaine- and amphetamine-regulated transcript peptide (CART)</td>
</tr>
<tr>
<td>Galanin</td>
<td>Peptide YY (3–36)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Opioids</td>
<td>CGRP</td>
</tr>
<tr>
<td>Alpha2-noradrenergic</td>
<td>Insulin</td>
</tr>
<tr>
<td>GABA</td>
<td>Prolactin-releasing peptide</td>
</tr>
<tr>
<td>GH-RH</td>
<td>Somatostatin</td>
</tr>
<tr>
<td>Opioid peptides</td>
<td>Cholecystokinin</td>
</tr>
<tr>
<td></td>
<td>Glucagon-like peptide-1 and -2</td>
</tr>
</tbody>
</table>

<sup>a</sup>Secreted mainly from stomach and acts on the hypothalamus  
<sup>b</sup>Secreted mainly from adipocytes and acts on the hypothalamus  
<sup>c</sup>Secreted mainly from intestines and acts on the hypothalamus
peptide family together with PP and peptide YY (PYY) [149]. In the peripheral tissues, NPY is localized in the sympathetic nerves, adrenal medulla, etc., and is one of the most potent vasoconstrictor peptides. NPY is the most abundantly expressed neuropeptide in the brain. In the human hypothalamus, NPY is localized in the infundibular nucleus (Fig. 2.15) and paraventricular nucleus [150]. NPY in the infundibular nucleus has been shown to act as a potent stimulator on appetite [151].

MCH was originally isolated from the salmon pituitary as a skin-color regulating hormone [152]. MCH has an antagonistic action against α-MSH, and make the skin color white by aggregating melanosome within melanophores in fishes. MCH is expressed predominantly in the hypothalamus of the mammals and acts as a neurotransmitter or a neuromodulator [153, 154]. MCH-containing perikarya are found in the posterior and lateral hypothalamic areas, particularly around the mammillary body and fornix (posterior nucleus and perifornical nucleus) (Fig. 2.16). MCH expression was increased in obese mice (ob/ob mice) and the central injection of MCH increased the feeding in rats [155]. Recent studies have shown that MCH knockout mice had reduced body weight [156], supporting a role of MCH as an appetite-stimulator. There are at least two subtypes of MCH receptors, MCH receptor 1 and 2, which are distinct from the melanocortin receptors (receptors for ACTH and/or α-MSH) [157–159]. Other appetite-stimulating hormone, orexins (hypocretins) [160, 161] are also expressed in the similar areas of hypothalamus to MCH, but rarely co-localize with MCH in the same neurons [162].

**Fig. 2.15** NPY in the human hypothalamus. NPY immunoreactive cell bodies are localized in the infundibular nucleus. Bar = 50 μm

**Fig. 2.16** MCH in the human hypothalamus. MCH immunoreactive cell bodies are exclusively localized in the posterior and lateral hypothalamic areas (LHA), including perifornical nucleus (PFN) (a) and posterior nucleus (b). 3rd V Third ventricle; MB mammillary body. Several photographs are combined. MCH-immunoreactive nerve fibers derived from these hypothalamic neurons are distributed throughout in the brain and pituitary. Bar = 200 μm
α-MSH is generated from the pre-opiomelanocortin (POMC), the common precursor protein with ACTH and endorphins, by post-translational enzymatic proteolytic processing. α-MSH corresponds to the N-terminal 1–13 portion of ACTH. The POMC neurons are present in the infundibular nucleus of hypothalamus. α-MSH expressed in this nucleus acts as a potent inhibitor on appetite [163]. There are at least five subtypes of melanocortin receptors. The melanocortin-1 receptor mediates an action of α-MSH on melanocytes, and the melanocortin-2 receptor mediates an action of ACTH on the adrenal cortex to produce and secrete glucocorticoids. The melanocortin-3 and -4 receptors mediate suppressive actions of α-MSH on appetite in the brain, particularly in the hypothalamus. Agouti protein is expressed in the mouse skin and regulates coat color by binding to and antagonizing the melanocortin-1 receptor. Agouti-related protein is a 132-amino acid protein with 25% homology to the Agouti protein [164]. Agouti-related protein is expressed in the infundibular nucleus of the hypothalamus and stimulates the appetite by antagonizing the actions of α-MSH on the melanocortin-3 and -4 receptors.

Ghrelin is secreted from the stomach and hypothalamus [13]. In addition to the GH-release activity, ghrelin has appetite-stimulating actions. It has been shown that both intracerebroventricular and intraperitoneal administration of ghrelin in rats stimulates food intake [14, 165]. Thus, not only ghrelin of the hypothalamic source, but also ghrelin secreted from the stomach, are supposed to act on the hypothalamus and stimulate appetite. Blockade of the vagal afferent pathway abolishes ghrelin-induced feeding, indicating that the vagal afferent pathway may be a route conveying orexigenic ghrelin signals to the brain [166]. Moreover, peripheral ghrelin signaling, which travels to the nucleus tractus solitarius (NTS) at least in part via the vagus nerve, increases noradrenaline in the arcuate nucleus of the hypothalamus, thereby stimulating feeding at least partially through alpha-1 and beta-2 noradrenergic receptors [167]. Plasma concentrations of ghrelin are high during fasting whereas they fall to a nadir within an hour of eating [168], suggesting a role of ghrelin in meal initiation.

Figure 2.17 shows the schematic representation of the putative relationship among leptin, ghrelin, and appetite-stimulating and inhibiting neuropeptides in the hypothalamus. Leptin receptor is expressed in the arcuate nucleus (infundibular nucleus), where leptin appears to regulate the secretion of appetite-stimulating and inhibiting neuropeptides, such as NPY and α-MSH.

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**Fig. 2.17** Schematic representation of the putative relationship between peripheral signals (adipokines such as leptin, and gut hormones) and brain (neuropeptides in the hypothalamus, etc.) in the appetite control. Appetite-stimulating and inhibiting factors are shown in blue and red, respectively. Leptin secreted from adipocytes and gut hormones such as ghrelin and PYY act on brain via the systemic circulation as circulating hormones (shown by red arrows) or via the vagal nerve (shown by a black arrow). There are complex neural networks among the hypothalamus, the brain stem, the cerebral cortex and other brain areas, and among the nuclei in the hypothalamus. CART cocaine- and amphetamine-regulated transcript; AGRP Agouti-related protein.
### 2.12.1 Genetic Diseases Associated with Obesity Related to Hypothalamus

Obesity is caused under the influence of many environmental factors and genetic predisposition in most cases. Recent studies have shown that certain types of obesity are caused by mutations in the single gene encoding the hormone, the hormone receptor, or the processing enzyme, which are related to the appetite regulation in the hypothalamus (Table 2.6). Obesity caused by melanocortin-4 receptor gene mutations is the most prevalent among the monogenic forms of inherited obesity. However, melanocortin-4 receptor gene mutations have been found in only 3–5% of obese patients, indicating that the monogenic forms of inherited obesity are very rare. The vast majority of obesity is considered to be caused by a polygenic disorder. Association of single-nucleotide polymorphisms in the secretogranin III gene with obesity was found in the Japanese populations [169]. Secretogranin III belongs to a family of acidic secretory proteins, known as granins, which are widely expressed in endocrine and neuronal cells, including the hypothalamic neurons and pancreatic β-cells, and participates in the secretion of neuropeptides and peptide hormones.

#### 2.12.1.1 Obesity Due to Single-Gene Mutations

**Mutations in the Gene of Leptin or Leptin Receptor**

Montague et al. [141] reported two severely obese children who are members of the same highly consanguineous pedigree in Pakistan. Their serum leptin levels were very low despite their markedly elevated fat mass. Homozygous frame-shift mutation involving the deletion of a single guanine nucleotide in codon 133 of the gene for leptin was found in both subjects. Strobel et al. reported that sequencing of the leptin gene from a Turkish obese patient with a low serum leptin level uncovered a missense mutation in codon 105, which led to the substitution of an Arg for Trp at position 84 of the mature protein [142]. Although a normal size leptin protein is synthetized in this subject, this is not secreted in serum. Patients with leptin deficiency showed multiple endocrine defects, decreased sympathetic tone, and immune system dysfunction [170]. The endocrine defects include hypogonadism, impaired renin-aldosterone function, and alterations in GH and PTH-calcium function.

Clement et al. reported a homozygous mutation in the human leptin receptor gene that resulted in a truncated leptin receptor lacking both the transmembrane and the intracellular domains [143]. In addition to their early onset morbid obesity, patients homozygous for this mutation have no pubertal development and their secretion of growth hormone and thyrotropin is reduced.

**Mutations in the Gene of the POMC or Melanocortin Receptors**

Kruide et al. reported cases of a genetic defect within the POMC gene that showed early onset obesity, adrenal insufficiency, and red hair pigmentation [171]. Patient 1 was found to be a compound heterozygote for two mutations in exon 3 (G7013T, C7133del) which interfere with appropriate synthesis of ACTH and α-MSH. Patient 2 was homozygous for a mutation in exon 2 (C3804A) which abolishes POMC translation. α-MSH has dual role in regulating food intake in the hypothalamus and influencing hair pigmentation, and therefore the deficiency of α-MSH results in obesity and red hair pigmentation. The deficiency in ACTH results in secondary adrenal insufficiency. POMC gene knockout mice lacking the POMC-derived peptides have obesity, defective adrenal development, and altered pigmentation; phenotypes similar to those of the human POMC-deficient patients [172].

The melanocortin-3 and -4 receptors mediate the suppressive actions of α-MSH on appetite in the hypothalamus. Vaisse et al. reported two families with frame shift mutations in melanocortin-4 receptor gene that caused an early onset in the dominant form of obesity [173]. Subsequent studies have shown that melanocortin-4 receptor gene mutations are a frequent but heterogeneous genetic cause of morbid obesity [174, 175]. Thus, melanocortin-4 receptor gene mutations may be the most frequent causes for obesity among patients with obesity due to single-gene mutations. A mutation (Ile183Asn) in the melanocortin-3 receptor gene was also found in obese subjects [176].

<table>
<thead>
<tr>
<th>Genes</th>
<th>Mechanism to cause obesity</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanocortin-4 receptor</td>
<td>Deficiency of α-MSH action to suppress the appetite in the hypothalamus</td>
<td>[173–175]</td>
</tr>
<tr>
<td>Melanocortin-3 receptor</td>
<td>Deficiency of α-MSH action to suppress the appetite in the hypothalamus</td>
<td>[176]</td>
</tr>
<tr>
<td>POMC</td>
<td>Deficiency of α-MSH secretion in the infundibular nucleus of hypothalamus</td>
<td>[171]</td>
</tr>
<tr>
<td>Leptin</td>
<td>Deficiency of functioning leptin secretion by adipocytes</td>
<td>[141, 142]</td>
</tr>
<tr>
<td>Leptin receptor</td>
<td>Deficiency of leptin action to suppress the appetite in the hypothalamus</td>
<td>[143]</td>
</tr>
<tr>
<td>Prohormone convertase 1</td>
<td>Deficiency of α-MSH processing in the infundibular nucleus of hypothalamus and insulin processing in the pancreatic β-cells (?)</td>
<td>[144, 145]</td>
</tr>
</tbody>
</table>
Mutations in the Gene of Prohormone Convertase 1

Prohormone convertase 1 is the endopeptidase which is expressed in the neuroendocrine tissues and processes the prohormones, including proinsulin and POMC. A patient with prohormone convertase 1 deficiency showed an extreme obesity, abnormal glucose homeostasis, hypogonadotropic hypogonadism, hypocortisolism, and elevated plasma proinsulin and POMC concentrations but very low plasma levels of insulin and ACTH [144]. The analysis of prohormone convertase 1 gene of this patient showed that this proband is a compound heterozygote for mutations in the prohormone convertase 1 gene [145].

2.12.1.2 Other Genetic Diseases Associated with Obesity

Bardet-Biedle Syndrome

Bardet-Biedl syndrome is an autosomal recessive disorder that is characterized by retinitis pigmentosa, polydactyly, obesity, mental retardation, hypogonadism, renal dysplasia, and short stature [177]. This disorder is heterogenous and at least four gene loci responsible for this disorder (BBS1-4) have been mapped: 11q13 (BBS1), 16q21 (BBS2), 3p12 (BBS3), and 15q22 (BBS4). Laurence-Moon syndrome and Bardet-Biedle syndrome are now regarded as distinct entities [178]. Laurence-Moon syndrome, however, is associated with spastic paraplegia.

Prader-Willi Syndrome

Prader-Willi syndrome is a genetic disorder characterized by a range of mental and physical symptoms [179]. These include short stature, muscular hypotonia, excessive appetite with progressive obesity, hypogonadism, mental retardation, behavioral abnormalities, sleep disturbances (including sleep apnea), and dysmorphic features. Prader-Willi syndrome is the most frequent cause of syndromic obesity occurring in one in 10,000–25,000 births. Occurring in 70–75% of affected individuals, the principal genetic mutation associated with the condition is deletion of a segment of the paternally derived chromosome 15 (15q11-q13). Several other abnormalities have also been linked with the syndrome: 20–25% of patients exhibit maternal disomy of the same region of chromosome 15, 2–5% have imprinting center mutations, and 1% have translocations. The individual gene or genes from within 15q11-q13 that cause the condition have yet to be identified.

The reduced GH secretion and hypogonadotropic hypogonadism occur in the majority of patients with Prader-Willi syndrome, together with abnormal appetite control and high pain threshold. This suggests that patients with Prader-Willi syndrome have hypothalamic-pituitary dysfunction. Autopsies of five patients with Prader-Willi syndrome showed that the paraventricular nucleus was reduced in size and there were fewer oxytocin-expressing neurons [180]. There were a 30% reduction in GH-RH-releasing neurons in the arcuate nucleus, a down-regulation of NPY, and a deficiency in vasopressin [181]. Magnetic resonance imaging has revealed a complete absence or a small size of the bright spot in the posterior pituitary lobe of four of 15 affected individuals, which is considered to be a sign of hypothalamic dysfunction [182]. Plasma ghrelin levels in children with Prader-Willi syndrome are elevated [183], and may be related to the pathogenesis of abnormal appetite control.

2.12.2 Obesity Due to Non-genetic Hypothalamic Causes

2.12.2.1 Frolich’s Syndrome

Frolich’s syndrome (adiposogenial dystrophy) was originally characterized as delayed puberty, hypogonadism, and obesity associated with a tumor that impinges on the hypothalamus [184]. Several organic lesions of the hypothalamus, however, can cause this disorder, including tumors, encephalitis, microcephaly, Friedrich’s ataxia, and demyelinating diseases.

2.12.3 Anorexia Nervosa

Anorexia nervosa is a functional disorder characterized by refusal to maintain body weight at or above a minimally normal weight for age and height, intense fear of gaining weight, a body image disturbance, and amenorrhea [185]. The etiology of this disorder is unknown. It occurs most often in young women.

Multiple endocrine disturbances and hypothalamic dysfunction are known to occur in patients with anorexia nervosa, which are as follows. Urinary and plasma levels of gonadotropins are low. Plasma cortisol levels and cerebrospinal fluid levels of CRH are elevated. This may be consistent with results in animal experiments showing that central administration of CRH decreases the feeding and the LH secretion.

Plasma GH levels are elevated whereas plasma levels of insulin-like growth factor I are decreased. Fasting plasma ghrelin levels were significantly higher in patients with anorexia nervosa than in normal age-matched female controls.
Therapeutic intervention in a psychosomatic institution caused a BMI increase and a significant decrease in circulating ghrelin levels. Thus, elevated plasma ghrelin may be a cause for the elevated plasma GH levels, and ghrelin resistance on the appetite may be present in cachectic states.

Plasma levels of leptin are reduced with low weight and the percentage of body fat in subjects with anorexia nervosa [187]. It has been shown that leptin has a stimulatory action on hypothalamic-pituitary-gonadal axis [188], raising the possibility that hypogonadism associated with anorexia nervosa is partly due to the leptin deficiency. On the other hand, the hypothalamic dysfunction with multiple endocrine disturbances seen in anorexia nervosa may be secondary phenomena due to the unknown central disturbance.

2.13 Narcolepsy and Orexins (Hypocretins)

Narcolepsy is a disabling neurological disorder that affects more than 1 in 2,000 individuals. This disorder is characterized by daytime sleepiness, sleep fragmentation, and symptoms of abnormal REM sleep, such as cataplexy, sleep paralysis, and hypnagogic hallucinations [189]. Most human cases of narcolepsy occur sporadically and the disorder is generally believed to be multifogenic and environmentally influenced, whereas in canine (Doberman pinschers) the disorder is transmitted as a single autosomal recessive trait. One predisposing genetic factor in human narcolepsy is a specific HLA-DQ allele, HLA-DQB1*0602. Because of the tight HLA association, the human narcolepsy was suggested to be autoimmune in nature. Recent studies have shown that neuropeptides, orexins (hypocretins), are involved in the pathogenesis of narcolepsy [189–192].

The orexins consist of two peptides: orexin-A, a 33-amino acid peptide and orexin-B, a 28-amino acid peptide, which are derived from the same precursor by proteolytic processing [160, 161]. The orexins are named following their central appetite-stimulating action. These peptides are specifically expressed in the hypothalamus, and the positive cell bodies are mostly restricted to the posterior hypothalamus. The actions of orexins are mediated by two G protein-coupled receptors named orexin-1 receptor and orexin-2 receptor.

Canine narcolepsy has been shown to be caused by a mutation in the orexin receptor 2 gene [189]. Transgenic mice with ablation of orexin-containing neurons showed a phenotype strikingly similar to human narcolepsy, including behavioral arrests, premature entry into REM sleep and poorly consolidated sleep patterns [190]. In most human cases of narcolepsy, orexin levels in the cerebrospinal fluid have been shown to be decreased to undetectable levels [191]. Studies using postmortem brain obtained from patients with narcolepsy showed loss of orexins in the posterior and lateral hypothalamic areas, without gliosis or signs of inflammation [192]. On the other hand, one orexin mutation, impairing peptide trafficking and processing, was found in a single case with early onset of narcolepsy among 74 patients. Although orexin loci do not contribute significantly to genetic predisposition, most cases of narcolepsy are associated with a deficient orexin system.

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