The Hypothalamus

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Development

• In the early embryo, neuroectoderm of the forebrain (prosenecephalon) primary brain vesicle divides to form two secondary brain vesicles, telencephalon (endbrain, cortex) and diencephalon.

• From the diencephalon ventro-lateral wall, intermediate zone proliferation generates the primordial hypothalamus.
The ventromedial nucleus (VMH) of the hypothalamic core, differentiates from neuroblasts at a time-point intermediate to the earlier differentiation of lateral hypothalamic nuclei and later differentiation of the midline nuclei (suprachiasmatic [SCN], arcuate, and paraventricular nuclei [PVH]).
ANATOMY

• The hypothalamus is located below the thalamus, just above the brainstem.

• Forms the ventral part of the diencephalon.

• BOUNDARIES:-

  – Anterior- optic chiasm,

  – laterally - sulci formed with the temporal lobes,

  – posteriorly by the mammillary bodies
• The smooth, rounded base of the hypothalamus is the tuber cinereum.
• The pituitary stalk descends from the median eminence.
• The median eminence stands out from the rest of the tuber cinereum because of its dense vascularity, which is formed by the primary plexus of the hypophyseal-portal system.
• The long portal veins run along the ventral surface of the pituitary stalk.
Inputs

• External environment - light, pain, temperature, odorants

• Internal environment - blood pressure, blood osmolality, blood glucose levels

• Neuroendocrine control – hormones - Glucocorticoids, estrogen, testosterone, thyroid hormone
• Provides coordinated responses through motor outputs to key regulatory sites.

• The patterned hypothalamic outputs to these effector sites ultimately result in coordinated endocrine, behavioral, and autonomic responses that maintain homeostasis.

• As part of the limbic system, it has connections to other limbic structures including the amygdala and septum.
HYPOTHALAMIC-PITUITARY UNIT

• Allows mammals to maintain homeostasis
• Destruction of the hypothalamus is not compatible with life.
• Hypothalamic control of homeostasis stems from the ability of this collection of neurons to orchestrate coordinated endocrine, autonomic, and behavioral responses.
HYPOTHALAMO – PITUTARY UNIT

• Posterior pituitary -nerve signals that originate in the hypothalamus

• Anterior pituitary -hypothalamic releasing and hypothalamic inhibitory hormones (or factors) - hypophysial portal vessels.

• In the anterior pituitary, these releasing and inhibitory hormones act on the glandular cells to control their secretion.
Figure 75–4

Hypothalamic-hypophysial portal system.
### Hypothalamic Factors:

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Target Cell (hormone)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GH releasing hormone (GHRH)</td>
<td>Somatotrope (+) GH</td>
</tr>
<tr>
<td>Somatostatin (SRIF)</td>
<td>Somatotrope (-) TSH</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Lactotrope (-) PRL</td>
</tr>
<tr>
<td>Thyrotropin releasing hormone</td>
<td>Lactotrope (+) PRL</td>
</tr>
<tr>
<td>Gonadotropin releasing hormone</td>
<td>Gonadotropes (+) FSH</td>
</tr>
<tr>
<td>Corticotropin (CRH)</td>
<td>Corticotrope (+) ACTH</td>
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</tbody>
</table>

### Hormones released into blood:

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Hormone</th>
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<tbody>
<tr>
<td>Acidophils</td>
<td>Growth Hormone (GH)</td>
</tr>
<tr>
<td>Lactotropes</td>
<td>Prolactin (PRL)</td>
</tr>
<tr>
<td>Basophils</td>
<td>Thyrotropin (TSH)</td>
</tr>
<tr>
<td>Thyrotropes</td>
<td>Folliculotropin (FSH) or</td>
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<tr>
<td>Gonadotropes</td>
<td>Luteotropin (LH)</td>
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<tr>
<td>Corticotropes</td>
<td>Corticotropin (ACTH)</td>
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<td></td>
<td>Melanocyte Stim. Hormone (MSH)</td>
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</table>

### Hormones released at nerve terminals:

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Target tissues:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasopressin (ADH)</td>
<td>Kidney, vasculature</td>
</tr>
<tr>
<td>Oxytocin</td>
<td>Mammary gland, uterus</td>
</tr>
</tbody>
</table>
Hypophysiotropic Hormones

• Regulation of pituitary hormones by the hypophysiotropic hormones is quite complex because of:
  – the multiplicity of substances present in the hypothalamus that can affect pituitary hormone secretion
  – the redundancy and overlapping nature of the feedback loops
• present in extrahypothalamic brain tissue and function as neurotransmitters.
• the action is mediated first by binding to specific receptors and then by alteration of intracellular transduction mechanisms
Thyrotropin-Releasing Hormone

- Secretion is stimulated by norepinephrine and dopamine
- Inhibited by serotonin.
- Function
  - stimulate the synthesis and release of thyroid-stimulating hormone (TSH) and prolactin.
The hypothalamus secretes Thyrotropin-releasing hormone (TRH), which stimulates the anterior pituitary gland to produce Thyroid-stimulating hormone (TSH). TSH then acts on the thyroid gland, stimulating the production of Thyroid hormones (T3 and T4). These hormones have various effects, including increased metabolism, growth and development, and increased catecholamine effect.
— stimulate growth hormone (GH) secretion in patients with acromegaly, as well as in several states associated with decreased insulin-like growth factor-I (IGF-I) feedback on GH secretion, such as cirrhosis, renal insufficiency, anorexia nervosa, poorly controlled type 1 diabetes mellitus, and malnutrition.

— Stimulates follicle-stimulating hormone (FSH) secretion in some patients with gonadotroph adenomas.
Gonadotropin-Releasing Hormone

- GnRH neurons originally develop in the epithelium of the medial part of the olfactory placode.
- The primary function of GnRH is to stimulate the secretion of luteinizing hormone (LH) and FSH.
- GnRH secretion is stimulated by dopamine and norepinephrine and is inhibited by serotonin.
- Kallmann's syndrome- GnRH deficiency is associated with anosmia secondary to agenesis of the olfactory bulbs.
• The hypothalamic effect is alteration of GnRH pulse amplitude and frequency, and the pituitary effect is modulation of the gonadotropin response to GnRH.

• In the follicular phase of the menstrual cycle, estrogen feeds back negatively on gonadotropin secretion.

• At midcycle, estrogen feedback becomes positive, and rising estrogen levels from the developing follicle stimulate the ovulatory surge of LH and FSH.

• Following ovulation, the feedback again becomes negative, and the estrogen and progesterone produced by the corpus luteum result in decreasing levels of LH and FSH.
• In men, testosterone decreases GnRH pulsatile secretion, with a resultant decline in gonadotropin pulse amplitude and frequency, as well as a diminished gonadotropin response to exogenous GnRH.
Somatostatin

- also known as somatotropin release–inhibiting factor

- Blocks the rise in GH in a dose-dependent fashion.

- GH secretory episodes are associated with increased GHRH secretion, often accompanied by low somatostatin levels;

- The basal or trough GH levels are associated with low GHRH concentrations and more elevated somatostatin levels.

- Inhibits basal and stimulated TSH secretion.

- Present — D cells of the pancreatic islets, the gut mucosa and myenteric neural plexus.
• somatostatin suppresses:
  – the secretion of insulin, glucagon, cholecystokinin, gastrin, secretin, vasoactive intestinal polypeptide (VIP), and other gastrointestinal hormones,
  – gastric acid secretion, gastric emptying, gallbladder contraction, and splanchnic blood flow.
• Analogues of somatostatin - treatment of acromegaly, carcinoid tumors, VIP-secreting tumors, TSH-secreting pituitary tumors, islet cell tumors, and diarrhea of numerous causes.
Corticotropin-Releasing Hormone

- Releases adrenocorticotropic hormone (ACTH), β-endorphin, β-lipotropin, melanocyte-stimulating hormone (MSH), and other peptides generated from proopiomelanocortin (POMC) in equimolar amounts.
- CRH mediates 75% of the ACTH response to stress, and the remaining 25% is mediated by vasopressin.
- CRH and vasopressin have synergistic effects on ACTH release.
- Cortisol feeds back to decrease ACTH secretion at both the hypothalamic and the pituitary levels.
• ACTH and β-endorphin also feed back negatively to decrease CRH release by the hypothalamus.

• Morphine suppresses the ACTH response to CRH, through opioid μ-receptors.

• Acetylcholine, dopamine, norepinephrine, and epinephrine stimulate and γ-aminobutyric acid inhibits hypothalamic CRH secretion.

• Norepinephrine and epinephrine also stimulate pituitary ACTH secretion directly and are additive to the stimulatory effect of CRH.
• Monokines released by inflammatory tissue, such as interleukin-1, interleukin-6, and tumor necrosis factor-α, stimulate the synthesis and release of CRH and vasopressin from the hypothalamus and the release of ACTH by the pituitary.

• The consequent increase in cortisol then reduces the intensity of the inflammatory response and release of these monokines, thus completing the feedback loop.

• Therefore, this neuroendocrine-immune loop serves to modulate the inflammatory response.
Growth Hormone–Releasing Hormone

- Stimulates GH secretion
- With repetitive administration every 3 hours, GHRH can cause the release of sufficient GH in children with GHRH deficiency to increase IGF-I levels and to accelerate growth.
- Both IGF-I and GH itself feed back negatively on GH secretion, with the negative feedback mediated by both a decrease in GHRH and an increase in somatostatin.
- High circulating GH levels that occur in IGF-I–deficient states -renal insufficiency and cirrhosis.
Prolactin-Inhibitory Factor

- The inhibitory component of hypothalamic regulation of prolactin secretion predominates over the stimulatory component.
- Dopamine is the major physiologic prolactin-inhibitory factor.
- Blockade of endogenous dopamine receptors by a variety of drugs, such as the neuroleptics, causes a rise in prolactin.
- Lesions that interrupt the basal hypothalamic neuronal pathways carrying dopamine to the median eminence or that interrupt portal blood flow, such as craniopharyngiomas or other large mass lesions, cause less dopamine to reach the pituitary and lead to hyperprolactinemia.
Prolactin-Releasing Factor

- Hypothalamic peptides other than TRH have also been shown to have PRF activity.
- VIP stimulates prolactin synthesis and release at concentrations found in hypothalamic-pituitary portal blood.
- Within the VIP precursor is another similarly sized peptide known as peptide histidine methionine, which also has PRF activity.
- Complicating the role of VIP as a PRF is the finding that VIP is actually synthesized by anterior pituitary tissue.
- The precise roles of VIP versus peptide histidine methionine and hypothalamic VIP versus pituitary VIP are still not clear.
DISEASES AFFECTING HYPOTHALAMUS
Pituitary Adenomas

• The most common tumor-pituitary adenomas that have significant suprasellar extension.

• Varying degrees of hypopituitarism, diabetes insipidus, and hyperprolactinemia.

• By compressing the normal pituitary or, more commonly, by affecting the pituitary stalk and mediobasal hypothalamus.

• Low serum prolactin level.

• Lack of TSH response to TRH.

• In patients with normal or elevated prolactin levels, pituitary function often returns following therapy.
Craniopharyngiomas and Rathke Cleft Cyst

- Craniopharyngiomas consist of cysts alternating with stratified squamous epithelium.
- The cyst fluid is usually thick and dark, and the material is often calcified.
- These tumors arise from remnants of Rathke's pouch.
- *Rathke cleft cyst*, develops from the space between the anterior and rudimentary intermediate lobes.
- Rathke's cleft cysts are lined with cuboidal as opposed to squamous epithelium, and the cyst fluid is usually a white, mucoid fluid.
• Mass effects- headache, vomiting, visual disturbance, seizures, hypopituitarism, and polyuria.

• Galactorrhea, amenorrhea, and hyperprolactinemia, features suggestive of a prolactinoma.

• testing reveals varying degrees of hypopituitarism in 50 to 75% and modest hyperprolactinemia in 25 to 50%.

• Surgical extirpation of craniopharyngiomas - a worsening of pituitary function, often resulting in complete panhypopituitarism and diabetes insipidus because of stalk section, and it may damage hypothalamic centers regulating thirst, body temperature, and food intake.
Suprasellar Dysgerminomas

- *Suprasellar dysgerminomas* arise from primitive germ cells that have migrated to the CNS during fetal life and are structurally identical to germ cell tumors of the gonads.
- decreased growth because of hypopituitarism
- diabetes insipidus, visual problems, Hyperprolactinemia
- precocious puberty - production of human chorionic gonadotropin by the tumor.
- The finding of an elevated human chorionic gonadotropin level in the spinal fluid is diagnostic.
- As opposed to craniopharyngiomas, these tumors are very radiosensitive, and radiation therapy is the preferred treatment.
Hamartoma

• A nodule of growth of hypothalamic neurons attached by a pedicle to the hypothalamus between the tuber cinereum and the mammillary bodies and extending into the basal cistern.

• Asymptomatic

• Enlarge and disrupt hypothalamic function because of compression of adjacent tissue.

• A variant of hamartoma consisting of similar tissue present within the anterior pituitary but without a neural attachment to the hypothalamus is called a choristoma or gangliocytoma.
• Can produce GnRH.

• surgery and with the administration of a long-acting GnRH analogue, which suppresses gonadotropin secretion but does not affect the tumor itself.

• If the hamartoma does not cause other problems from mass effects, medical therapy with the GnRH analogue may be the best choice.

• Some gangliocytomas have been reported that produced GHRH and acromegaly or CRH and Cushing's syndrome.
Other Tumors

- Other tumors and space-occupying lesions occurring in the suprasellar area include arachnoid cysts, meningiomas, gliomas, astrocytomas, chordomas, infundibulomas, cholesteatomas, neurofibromas, lipomas, and metastatic cancer (particularly from the breast and lung).

- Any such lesion may be manifested by varying degrees of hypopituitarism, diabetes insipidus, and hyperprolactinemia, and surgical therapy often worsens the hormonal deficit and may cause other hypothalamic damage.
Sarcoidosis

- CNS involvement in cases of *sarcoidosis* occurs in 1 to 5% of patients.
- Isolated CNS sarcoidosis is quite uncommon, however. When sarcoidosis does involve the CNS, the hypothalamus is affected in 10 to 20% of cases.
- Sarcoid granulomas can involve the hypothalamus, stalk, or pituitary and may be infiltrative or occur as a mass lesion.
- Rarely, sarcoid granulomas can be manifested as an expanding intrasellar mass mimicking a pituitary tumor.
• Varying degrees of hypopituitarism, diabetes insipidus, and hyperprolactinemia.

• Obesity secondary to hypothalamic involvement by sarcoidosis.

• Examination of cerebrospinal fluid usually shows elevated protein levels, low glucose levels, pleocytosis, and variable elevations of angiotensin-converting enzyme.

• Corticosteroid therapy - reverse the thirst disorders partially, anterior pituitary hormone deficits do not respond to treatment.
Langerhans Cell Histiocytosis

- Eosinophilic granulomatous infiltration of the hypothalamus may cause diabetes insipidus, hypopituitarism, and hyperprolactinemia.
- Most common cause of diabetes insipidus in children.
- Usually, this infiltration appears as a thickening of the pituitary stalk, but it may also appear as a mass lesion of the hypothalamus or the pituitary.
- Osteolytic lesions may be present in the jaw or mastoid.
- Therapy - local surgery, focal irradiation, or chemotherapy with alkylating agents and high-dose corticosteroids.
Vascular Disease

• An enlarging aneurysm may be manifested as a mass lesion of the hypothalamic-pituitary area and may cause hypopituitarism and visual field defects.

• Tumors and aneurysms may also coexist, and careful radiologic evaluation with MRI is necessary to discern such association.

• Hypothalamic disease caused by vascular infarction is extremely rare.
Trauma

• defects ranging from isolated ACTH deficiency to panhypopituitarism with diabetes insipidus.

• Within the first 72 hours of trauma, GH, LH, ACTH, TSH, and prolactin levels may actually be elevated in blood, because of acute release.

• These levels subsequently fall, and either pituitary function returns to normal or hypopituitarism develops.

• In patients dying of head injury, anterior pituitary infarction has been found in 16% of cases, posterior pituitary hemorrhage in 34%, and hypothalamic hemorrhage or infarction in 42% of cases.
• The paraventricular and supraoptic nuclei and median eminence are particularly involved with microhemorrhages, hence the high frequency of panhypopituitarism with diabetes insipidus.

• With frontal injuries, the brain travels backward but the pituitary cannot move; consequently, the pituitary stalk becomes avulsed, with interruption of the portal vessels.

• Most patients with head injury are hyperprolactinemic, a finding that clinically confirms that the hypothalamus or stalk is the primary site of injury.
Irradiation

- Whole brain irradiation for intracranial neoplasms
- Hyperprolactinemia, hypopituitarism
- must be monitored periodically for the purpose of detecting these deficits when they occur.
- The development of such deficiencies may take many years, so yearly testing is warranted for up to 20 years.
- stereotactic irradiation using the gamma knife apparatus or a linear accelerator for pituitary and other parasellar tumors causes a risk of hypopituitarism similar to that of conventional irradiation.
Effects of Hypothalamic Disease on Pituitary Function

- Hypothalamic disease can cause both pituitary hyperfunction and hypofunction in varying degrees of severity.
- The common finding of hyperprolactinemia occurring with hypothalamic dysfunction causes hypogonadotrophic hypogonadism that is reversible when the elevated prolactin levels are brought down to normal.
• Loss of normal GH secretion is the most common hormonal defect occurring with structural hypothalamic disease.
• Congenital idiopathic GH deficiency is a heterogeneous disorder consisting of hypothalamic and pituitary defects, and it has a reported incidence between 1 in 3500 and 1 in 10,000 live births.
• The diagnosis is usually made between 1 and 3 years of age because of impaired growth.
Hypothalamic Hypogonadism

Pathobiology

- The primary defect involves the secretion of GnRH, with resultant impairment in pituitary gonadotropin secretion and gonadal function.
- Depending on the time of onset, they are manifested as delayed puberty, interruption of pubertal progression, or loss of adult gonadal function.
- May have loss of other hormones or may be isolated to GnRH.
- Loss of gonadotropin secretion as the result of hypothalamic structural damage is the second most common defect after GH deficiency.
- However, many of these defects are the result of hyperprolactinemia and are reversible with correction of the hyperprolactinemia.
• prepubertally - failure of onset of puberty or incomplete progression of puberty.

• If the disorder is limited to GnRH and the gonadotropins, prior growth and development are normal, but the growth spurt occurring at puberty is lost.

• Undescended testes
Figure 7 - hormones and Kallmann's syndrome

- hypothalamus
- pituitary gland
- GnRH
- LH & FSH

"feedback" hormones

- testes
- ovaries

"feedback" hormones

sperm cells

testosterone

voice "breaks"
growth of muscle tissue
enlargement of genitalia
facial, pubic & axillary hair

egg cell

oestrogen

broadening of hips
menstruation begins
development of breasts
pubic & axillary hair
Treatment

- Replacement of GnRH by subcutaneous administration every 2 hours with a portable pump.
- This treatment causes a rapid rise in LH and FSH responses to GnRH, a rise in testosterone to normal, and the development of normal spermatogenesis in men.
- Similar approaches in women result in ovulatory cycles in 80%.
- Replacement with testosterone alone causes adequate androgenization but does not increase testicular size or enhance spermatogenesis.
Two goals in the treatment of idiopathic, functional hypogonadotrophic amenorrhea are

- (1) restoration of a normal estrogen status to promote well-being and to prevent osteoporosis and
- (2) facilitation of ovulation for fertility.

The former can generally be achieved with cyclic estrogen and progesterone, whereas the latter may require clomiphene or GnRH or gonadotropin therapy.

In men, similar goals may be achieved with testosterone or GnRH or gonadotropins.
Hypothalamic Hyperprolactinemia

Diagnosis

• Structural or infiltrative lesions of the hypothalamus, can decrease the amount of dopamine reaching the lactotrophs - hyperprolactinemia.

• Because their therapy is quite different, it is very important to differentiate nonsecreting pituitary adenomas with extensive suprasellar extension causing prolactin elevations in this range from prolactin-secreting adenomas, which, when of such a large size, usually cause prolactin elevations 5 to 50 times higher.

• Numerous medications, antipsychotic agents in particular, can cause hyperprolactinemia, primarily by interfering with central catecholamines.
Treatment

• directed at the underlying cause.

• The hyperprolactinemia itself may impair gonadal function, so efforts may also be made to lower prolactin levels with dopamine agonists.

• Both dopamine agonists and sex steroid replacement may be necessary.

• When administration of psychotropic medications that cause the hyperprolactinemia cannot be stopped, dopamine agonists may be used, but they may exacerbate the patient's psychosis.

• In such cases and in other patients in whom fertility is not an issue, treatment with cyclic estrogen and progestin replacement can be carried out safely.
Idiopathic Hyperprolactinemia

• diagnosis of exclusion.
• Prolactin levels in this condition are usually lower than 100 ng/mL.
• amenorrhea, galactorrhea, impotence, infertility, and loss of libido, just as occurs with hyperprolactinemia of other causes, so the condition may need to be treated.
• Premature osteoporosis related to the estrogen deficiency may also occur.
• treatment is with dopamine agonists and cyclic estrogen and progesterone replacement may be given, but fertility will not be restored.
Tertiary hypothyroidism

- central lesion that impairs the secretion of TRH, usually along with the loss of other hormones.
- TSH levels in this syndrome are generally normal
- TSH in these patients is biologically less active than normal and binds to the TSH receptor less well because of altered glycosylation as a result of the TRH deficiency.
- Treatment is with L-thyroxine and therapy is monitored solely by measurement of free thyroxine levels and not TSH levels
Adrenocorticotropic Hormone

Hypothalamic ACTH deficiency

- Basal ACTH levels are low, and the ACTH response to injected CRH may be prolonged and exaggerated.
- The best test - comparison of ACTH responses to hypoglycemia, which is clearly mediated by the hypothalamus, and to CRH.
- The ACTH response is low in response to hypoglycemia but is increased and delayed in response to CRH in most patients with hypothalamic CRH deficiency.
- Treatment is with glucocorticoids, and mineralocorticoids are not needed.
Vasopressin

- Diabetes insipidus can develop as a result of destructive lesions in the supraoptic and paraventricular nuclei or in the mediobasal hypothalamus in the path of the neural fibers containing vasopressin that are passing on to the posterior pituitary.

- Irritative lesions can trigger the release of vasopressin in an unregulated fashion and thereby can result in the syndrome of inappropriate antidiuretic hormone (vasopressin) secretion.
Effects of Hypothalamic Disease on Other Neurometabolic Functions
Hypothalamic Obesity

• Destruction of the mediobasal hypothalamus sometimes inhibits satiety and may result in hyperphagia and hypothalamic obesity.

• The hyperphagia is the result of destruction of noradrenergic fibers originating in the paraventricular nucleus and passing through the mediobasal hypothalamus.

• Because of their location, such lesions also usually produce hypopituitarism and diabetes insipidus.

• Prader-Willi syndrome is the most common and occurs in 1 in 25,000 births.
Prader-Willi syndrome

• It is characterized by hypotonia, obesity, short stature, mental deficiency, hypogonadism, and small hands and feet.

• Approximately 70% of patients have a chromosome 15 deletion (15q11-q13) on the paternally derived chromosome.

• In the few cases studied at autopsy, no discernible hypothalamic lesions were detected.

• In the other syndromes (Laurence-Moon-Biedl-Bardet, Alström-Hallgren), no specific hypothalamic lesions have been found.
Hypothalamic Anorexia

- Lesions of the lateral hypothalamus, which destroy nigrostriatal dopaminergic fibers that pass through this area, produce hypophagia along with an increase in peripheral norepinephrine turnover and metabolic rate.

- very rare, owing to the requirement of bilateral lesions.

- All the hormonal changes that occur in anorexia nervosa appear to be secondary to the weight loss, and no evidence for a primary hypothalamic disorder in this syndrome has been found.
• Hypothalamic activation as part of the generalized response to stress can cause release of GH, prolactin, and ACTH, which serve as counterregulatory hormones with respect to insulin.

• These hormones promote lipolysis, gluconeogenesis, and insulin resistance, with resulting glucose elevation.

• Of more importance in the acute response to stress, this hypothalamic response results in sympathetic activation with release of catecholamines that inhibit insulin secretion and stimulate glycogenolysis.

• In rare circumstances of acute hypothalamic injury from trauma, stroke, or infection, severe hyperglycemia can occur.
Temperature Regulation

- The anterior hypothalamus and preoptic area contain temperature-sensitive neurons that respond to internal temperature changes by initiating certain thermoregulatory responses necessary to restore a constant temperature.

- Measures that dissipate heat include cutaneous vasodilation, sweating, panting, and behavioral changes that result in attempts to alter the environment.

- Measures that increase body heat include increasing metabolic heat production, shivering, cutaneous vasoconstriction, and similar behavioral changes.
Eating Disorders
• The eating disorders are psychiatric syndromes characterized by abnormal eating behaviors and maladaptive thoughts or beliefs about eating, shape, or weight.

• The American Psychiatric Association’s *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)* describes two primary eating disorders, anorexia nervosa (AN) and bulimia nervosa (BN).
Epidemiology

- Among women - the lifetime prevalence 1%.
- Much less common in males.
- More prevalent in cultures where food is plentiful and being thin is associated with attractiveness.
- Individuals who pursue interests that place a premium on thinness, such as ballet and modeling, are at greater risk.
<table>
<thead>
<tr>
<th><strong>TABLE 226-1</strong> DSM-IV-TR* DIAGNOSTIC CRITERIA FOR ANOREXIA NERVOSA</th>
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</thead>
<tbody>
<tr>
<td>A. Refusal to maintain body weight at or above a minimally normal weight for age and height (e.g., weight loss leading to maintenance of body weight less than 85% of that expected; or failure to make expected weight gain during period of growth, leading to body weight less than 85% of that expected).</td>
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<tr>
<td>B. Intense fear of gaining weight or becoming fat, even though underweight.</td>
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<td>C. Disturbance in the way in which one’s body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of the current low body weight.</td>
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<tr>
<td>D. In postmenarchal females, amenorrhea, that is, the absence of at least three consecutive menstrual cycles (a woman is considered to have amenorrhea if her periods occur following only hormone, e.g., estrogen, administration).</td>
</tr>
</tbody>
</table>

**Specify type:**

**Restricting type:** During the current episode of anorexia nervosa, the person has not regularly engaged in binge eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas).

**Binge-eating/purging type:** During the current episode of anorexia nervosa, the person has regularly engaged in binge eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas).

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• severe electrolyte imbalances, should be identified and addressed.

• Nutritional restoration - accomplished by oral feeding, and parenteral methods are rarely required.

• For severely underweight patients, sufficient calories (approximately 1200–1800 kcal/d) should be provided initially in divided meals as food or liquid supplements to maintain weight and permit physiological stabilization.
• Calories can then be gradually increased to achieve a weight gain of 1–2 kg (2–4 lb) per week, typically requiring an intake of 3000–4000 kcal/d.

• Patients have great psychological difficulty complying with the need for increased caloric consumption, and the assistance of psychiatrists or psychologists experienced in the treatment of AN is usually necessary.
• Psychiatric treatment focuses primarily on two issues.
• First, patients require much emotional support during the period of weight gain.
• Second, patients must learn to base their self-esteem not on the achievement of an inappropriately low weight, but on the development of satisfying personal relationships and the attainment of reasonable academic and occupational goals.
Bulimia Nervosa

Epidemiology

• In women, the full syndrome of BN occurs with a lifetime prevalence of 1–3%.

• Variants of the disorder, such as occasional binge eating or purging, are much more common and occur in 5–10% of young women.

• The frequency of BN among men is less than one-tenth of that among women.
Etiology

• Multifactorial
• higher-than-expected prevalence of childhood and parental obesity - suggesting that a predisposition toward obesity may increase vulnerability to this eating disorder.
• The marked increase in the number of cases of BN during the past 30 years and the rarity of BN in underdeveloped countries imply that cultural factors are important.
<table>
<thead>
<tr>
<th>TABLE 226-2 DSM-IV-TR* DIAGNOSTIC CRITERIA FOR BULIMIA NERVOSA</th>
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<tbody>
<tr>
<td>A. Recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following:</td>
</tr>
<tr>
<td>1. Eating, in a discrete period of time (e.g., within any 2-hour period), an amount of food that is definitely larger than most people would eat during a similar period of time and under similar circumstances.</td>
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<tr>
<td>2. A sense of lack of control over eating during the episodes (e.g., a feeling that one cannot stop eating or control what or how much one is eating).</td>
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<tr>
<td>B. Recurrent inappropriate compensatory behavior in order to prevent weight gain, such as self-induced vomiting; misuse of laxatives, diuretics, enemas, or other medications; fasting; or excessive exercise.</td>
</tr>
<tr>
<td>C. The binge eating and inappropriate compensatory behaviors both occur, on average, at least twice a week for 3 months.</td>
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<tr>
<td>D. Self-evaluation is unduly influenced by body shape and weight.</td>
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<tr>
<td>E. The disturbance does not occur exclusively during episodes of anorexia nervosa.</td>
</tr>
<tr>
<td>Specify type:</td>
</tr>
<tr>
<td><strong>Purging type:</strong> During the current episode of bulimia nervosa, the person has regularly engaged in self-induced vomiting or the misuse of laxatives, diuretics, or enemas.</td>
</tr>
<tr>
<td><strong>Nonpurging type:</strong> During the current episode of bulimia nervosa, the person has used other inappropriate compensatory behaviors, such as fasting or excessive exercise, but has not regularly engaged in self-induced vomiting or the misuse of laxatives, diuretics, or enemas.</td>
</tr>
</tbody>
</table>

*Diagnostic and Statistical Manual of Mental Disorders. 4th ed., text revision. Copyright 2000 American Psychiatric Association.*
Prognosis

- much more favorable than that of AN.
- Mortality is low, and full recovery occurs in approximately 50% of patients within 10 years.
- Approximately 25% of patients have persistent symptoms of BN over many years.
- Few patients progress from BN to AN.
Treatment

- usually be treated on an outpatient basis.
- Cognitive behavioral therapy (CBT)
- Antidepressant medications- selective serotonin reuptake inhibitor fluoxetine
- Antidepressant medications are helpful even for patients with BN who are not depressed, and the dose of fluoxetine recommended for BN (60 mg/d) is higher than that typically used to treat depression.
BINGE-EATING DISORDER

• BED is characterized by recurrent binge eating in the absence of regular, inappropriate compensatory behaviors.

• classified in DSM-IV-TR as an example of EDNOS.
EATING DISORDER NOT OTHERWISE SPECIFIED

- EDNOS is the most common diagnosis at many eating disorders programs, reflecting considerable fluidity in the presentation of disordered eating over time and the limitations of current diagnostic criteria.
- Many cases of EDNOS are subsyndromal variants of AN or BN, but there also are other patterns of disordered eating.
- For example, purging disorder, or recurrent purging behaviors in the absence of binge eating.
Hypothalamic Obesity

• Destruction of the mediobasal hypothalamus sometimes inhibits satiety and may result in hyperphagia and hypothalamic obesity.

• The hyperphagia is the result of destruction of noradrenergic fibers originating in the paraventricular nucleus and passing through the mediobasal hypothalamus.

• Because of their location, such lesions also usually produce hypopituitarism and diabetes insipidus.

• Prader-Willi syndrome is the most common and occurs in 1 in 25,000 births.
Prader-Willi syndrome

• It is characterized by hypotonia, obesity, short stature, mental deficiency, hypogonadism, and small hands and feet.

• Approximately 70% of patients have a chromosome 15 deletion (15q11-q13) on the paternally derived chromosome.

• In the few cases studied at autopsy, no discernible hypothalamic lesions were detected.

• In the other syndromes (Laurence-Moon-Biedl-Bardet, Alström-Hallgren), no specific hypothalamic lesions have been found.
Hypothalamic Anorexia

• Lesions of the lateral hypothalamus, which destroy nigrostriatal dopaminergic fibers that pass through this area, produce hypophagia along with an increase in peripheral norepinephrine turnover and metabolic rate.

• Very rare, owing to the requirement of bilateral lesions.

• All the hormonal changes that occur in anorexia nervosa appear to be secondary to the weight loss, and no evidence for a primary hypothalamic disorder in this syndrome has been found.
References

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- Textbook of Medical Physiology – Guyton and Hall
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