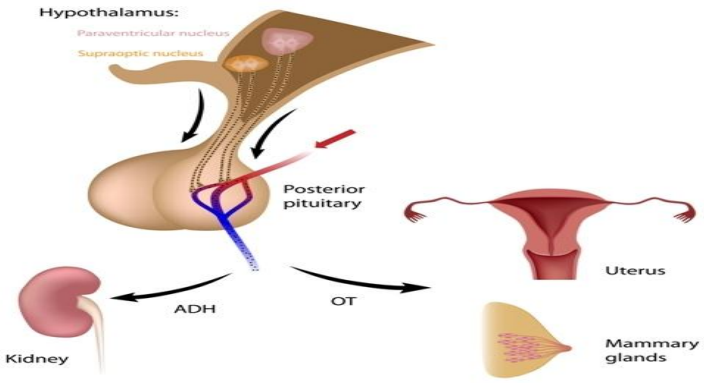
Disorders of the Hypothalamus & Pituitary Gland

The hypothalamus is the part of the brain where activity of the autonomic nervous system and endocrine glands, which directly control various systems of the body, is integrated with input from other centers that give rise to emotions and behavior.



The hypothalamus thus serves to ensure that

(1) The organism responds appropriately to deviations from various internal set points (including those for temperature, volume, osmolality, satiety, and body fat content).

(2) The responses to such deviations from a set point include coordinated activity of the nervous and endocrine systems.

(3) The emotions and behavior being manifested are appropriate for reflex responses being triggered to correct the deviations from internal set points. The following description outlines the integrative function of the hypothalamus in regard to the coordination of endocrine and CNS responses.

Intravascular volume loss from any cause activates autonomic neural responses, mainly via the sympathetic nervous system to retain fluid and electrolytes, maintain blood pressure through vascular smooth muscle contraction, and maintain cardiac output by increasing heart rate. The effect of these immediate neural responses is reinforced by activation of several hormonal systems. In response to a decrease in intravascular volume, the renin-angiotensin-aldosteronesystem (RAAS) is activated and sodium is retained. Additionally increasing osmolarity triggers thirst and leads to release of vasopressin (antidiuretic hormone [ADH]) from hypothalamic neurons that end in the posterior pituitary, resulting in free water absorption in the kidney. In short, the body maintains intravascular volume by regulating sodium reabsorption through aldosterone, while it

regulates osmolarity by increasing fluid intake (thirst) and free water retention by vasopressin.

Emotions interplay with these systems to coordinate appropriate behavioral and hormonal responses. Fear and pain activate limbic, hypothalamic and other centers to coordinate respective defensive (fight or flight) and recuperative stereotypic behaviors. These emotional responses to various stressors (eg, perceived threat to body; fear) also activate the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis, which coordinate the mammalian stress response through preparing the body for fight and flight and through mobilization of energy stores. Any kind of stress (eg, physical, mental, metabolic stress) leads to the release of corticotropin-releasing hormone (CRH) from the hypothalamus and consequent adrenocorticotropin (ACTH; pituitary) and cortisol (adrenal cortex) secretion. For example, starvation leads to the activation of the HPA axis and ultimately cortisol-mediated increased gluconeogenesis to maintain basic physiologic functions.

The pituitary gland is the partner of the hypothalamus on the body side of the mind-body interface. Once viewed as the “master gland” in regulation of neuroendocrine systems, the pituitary is now known to be a “middle manager” responding to input from both the brain (via the hypothalamus) and the body (via the various peripheral endocrine glands).

The basic framework for hypothalamic-pituitary function is the neuroendocrine axis, a cascade of interacting hormonal products from various regions of the CNS to the hypothalamus, anterior pituitary gland, peripheral endocrine end organs, and peripheral target tissues. Some neuroendocrine axes involve ..

DISORDERS OF ANTERIOR PITUITARY HORMONE SECRETION

The main clinical syndromes associated with excessive or deficient anterior pituitary hormone secretion. Excessive secretion usually involves a single hormone, but deficiencies are often multiple. However, many pituitary tumours are non-secretory and may present clinically with eye signs or headaches.

Growth hormone Growth hormone secretion from the anterior pituitary gland is mainly controlled by hypothalamic GH releasing hormone (GHRH). After synthesis by the hypothalamus, this is transported via the hypothalamic portal system to the somatotrophs of the anterior pituitary.

Secretion of GHRH, and therefore of GH, is pulsatile, occurring about seven or eight times a day, usually associated with: ● exercise, ● onset of deep sleep, ● in response to the falling plasma glucose concentration about an hour after meals. At other times, plasma concentrations are usually very low or undetectable, especially in children. Growth hormone release is inhibited in a negative feedback pathway by another hypothalamic hormone, somatostatin (GH-release inhibiting hormone). Somatostatin is found not only in the hypothalamus and in the brain, but also in the gastrointestinal tract and pancreatic islet cells, where it inhibits the secretion of many gastrointestinal hormones. Insulinlike growth factor 1 (IGF-1) acts by feedback to inhibit GHRH action.

Growth hormone secretion may be stimulated by:

- stress, one cause of which is hypoglycaemia,
- glucagon,
- some amino acids, for example arginine,
- drugs such as levodopa and clonidine.

All these stimuli have been used to assess GH secretory capacity, which may also be impaired in obese patients, in hypothyroidism and hypogonadism, in some cases of Cushing's syndrome and in patients receiving large doses of steroid

Actions of growth hormone:

The main function of GH is to promote growth. Its action is primarily mediated by IGFs, polypeptides that are synthesized in many tissues, where they act locally. Plasma concentrations of one of these, IGF-1 (also known as somatomedin C), correlate with GH secretion. Carbohydrate metabolism is affected by GH: GH antagonizes the insulin-mediated cell uptake of glucose, and excess secretion may produce glucose intolerance. Fat metabolism is stimulated by GH: lipolysis is stimulated, with a consequent increase in the concentration of circulating free fatty acids. Free fatty acid antagonizes insulin release and action. Growth hormone enhances protein synthesis, in conjunction with insulin, to stimulate amino acid uptake by cells. The production of IGF-1 is also influenced by other factors, the most important of which is nutritional status. In undernutrition, plasma concentrations are low, whereas GH concentrations are elevated, suggesting that plasma IGF-1 may influence

GH secretion by negative feedback. Other factors, such as adequate nutrition and T4, are also needed for normal growth. The growth spurt during puberty may be enhanced by androgens

Growth hormone excess: gigantism and acromegaly

Growth hormone excess causes gigantism during childhood and acromegaly in adults. Most patients with GH excess have acidophil adenomas of the anterior pituitary gland, which may be secondary to excessive hypothalamic stimulation. Rarely, malignant tumours may release GH or GHRH

Acromegaly is sometimes one of the manifestations of multiple endocrine neoplasia (MEN). The clinical manifestations of GH excess depend on whether the condition develops before or after fusion of the bony epiphyses.

Gigantism is caused by excess GH secretion in childhood before fusion of the epiphyseal plates, which may be delayed by accompanying hypogonadism. Heights of up to about 2 metres may be reached. Acromegalic features may develop after bony fusion, but these patients may die in early adult life from infection or cardiac failure or as a consequence of progressive pituitary tumour growth

An increase in the bulk of bone and soft tissues with enlargement of for example, the hands, tongue, jaw and heart. Changes in facial appearance are often marked, due to the increasing size of the jaw and sinuses; the gradual coarsening of the features may pass unnoticed for many years. Thyroid gland enlargement may be clinically detectable, but the patient is usually euthyroid.

● Excessive hair growth, hyperhidrosis and sebaceous gland secretion are common.

● Menstrual disturbances are common in females.

● Impaired glucose tolerance is present in about 25 per cent of patients, about half of whom develop symptomatic diabetes mellitus.

In most cases the pancreas can secrete enough insulin to overcome the .antagonistic effect of GH

●

There is a predisposition to multiple pre-malignant colon polyposis and hypertension.

● Hyperphosphataemia, hypercalcaemia and hypertriglyceridaemia may also be present. Many of these features are due to the action of IGF-1, which acts as a general growth factor. A different group of symptoms may occur due to the encroachment of a pituitary tumour on surrounding structures:

● Compression of the optic chiasma may cause visual field defects such as bitemporal hemianopsia.

● If destruction of the gland progresses, other anterior pituitary hormones such as ACTH, LH, FSH and TSH may become deficient (see above). Plasma prolactin concentrations may, however, be raised as prolactin differs from all other pituitary hormones in its method of control. Secretion is inhibited, not stimulated, by dopamine; therefore, .impairment of hypothalamic control causes hyperprolactinaemia

Diagnosis The diagnosis of GH excess is suggested by the clinical presentation, biochemical tests and radiological findings of the pituitary. Magnetic resonance imaging (MRI) is more sensitive than computerized tomography (CT) scanning. Plasma GH concentrations are usually higher than normal and may reach several hundred milliunits per litre (mU/L), but, because of the wide reference range, the results from ambulant patients may

Glucose suppression test for suspected acromegaly

Procedure After an overnight fast, insert an indwelling intravenous cannula. After at least 30 min, take basal samples for plasma glucose and GH estimation. The patient should drink 75 g of glucose dissolved in about 300 mL of water, or an equivalent glucose load. Take samples for

glucose and GH assays at 30, 60, 90 and 120 min after the glucose load .has been taken

Interpretation In normal subjects, plasma GH concentrations fall to undetectable levels. Although failure to suppress suggests acromegaly or gigantism, it may be found in some patients with severe liver or renal disease, in heroin addicts or in those taking levodopa. Fasting plasma GH can be normal in 8 per cent of acromegalic patients. The plasma glucose concentrations may demonstrate impaired glucose tolerance or diabetes mellitus in acromegaly.

Note //that the test is usually unnecessary in patients who are diabetic, as GH should already be suppressed. If acromegaly is confirmed, it is wise to investigate for other pituitary hormone defects, for example TSH, LH, FSH and ACTH. Acromegaly can also be associated with the MEN syndrome Plasma IGF-1 has a long half-life and may be used in screening for acromegaly. Plasma concentrations correlate with the activity of the disease. Measurement of the plasma concentrations of GH, or of IGF-1, may be used to monitor the efficacy of treatment. Remember that pregnancy increases IGF-1 concentration, and starvation, obesity and diabetes mellitus decrease it. Insulin-like growth-factor-binding protein-3 is the main binding protein for IGF-1 and its concentration is also increased in acromegaly. Sometimes plasma GHRH concentrations are useful and can be raised where there is an ectopic source or may be suppressed in pituitary disease. Computerized tomography or MRI body scanning may help to fi nd an ectopic source of GH or GHRH.

CASE 1 A 48-year-old man noticed that his hat size had increased, and his wife thought that his appearance had changed since their marriage, his features becoming coarser and his hands larger. Plasma insulin-like growth factor 1 (IGF-1) concentration was raised and an oral glucose suppression test was performed. The results were as follows: Plasma 0 minutes: GH 24.5 mg/L 30 minutes: GH 24.6 mg/L 60 minutes: GH 23.7 mg/L 90 minutes: GH 20.5 mg/L 120 minutes: GH 25.8 mg/L

DISCUSSION The plasma growth hormone (GH) concentration was not suppressed during the test in any of the samples. These findings are indicative of acromegaly; the clinical features are typical of acromegaly. This case illustrates the principle of using a suppression test when considering a condition involving a hormone excess. In healthy individuals, plasma GH concentration would be suppressed to less than

1 mg/L by the glucose intake

Growth hormone deficiency

In adults, GH deficiency may cause clinical symptoms, such as tiredness, dyslipidaemia and increased cardiovascular disease. Growth hormone defi ciency can cause short stature in children. It is present in a small percentage of normally proportioned small children: the birthweight may be normal but the rate of growth is subnormal. Other causes of growth retardation and short stature must be excluded before a diagnosis of GH defi ciency is made Turner's syndrome (45,X0) is suspected. There is a physiological reduction in GH secretion at the end of pre-puberty. Thus, in children with bone age more than 10 years, priming with sex hormones before investigation may be necessary. For example, ethinyloestradiol may be given to girls and testosterone to boys prior to testing. There is no general agreement about the best way to investigate such children biochemically. This is partly because GH secretion is episodic, GH assays vary between laboratories, and there is a variable response of GH to provocative stimuli. Plasma GH concentrations in normal children are often low and assays under basal

CASE 2

A 10-year-old boy was referred to the paediatric outpatient clinic because of short stature. His height was 1.08 m and he had normal body proportions. Physical examination and preliminary biochemical tests showed no obvious explanation for his small stature. A random plasma GH was less than 2 mg/L. After a glucagon stimulation test, the plasma GH concentration failed to increase above 2 mg/L. However, other .pituitary hormone concentrations were normal on biochemical testing

DISCUSSION A diagnosis of isolated GH deficiency was made. Note the failure of GH concentration to increase after stimulation by glucagon. This illustrates well the concept of using stimulation dynamic tests when considering a hormone deficiency state

Consequences of pituitary hormone deficiencies Progressive pituitary damage usually presents with evidence of deficiencies of gonadotrophins and GH. Plasma ACTH and/or TSH concentrations may remain normal, or become deficient months or even years later. The clinical and biochemical consequences of the target-gland failure include the following: ● Growth retardation in children This may be due to

deficiency of GH; deficiency of TSH, and therefore of thyroid hormone, may contribute

Secondary hypogonadism

This is due to gonadotrophin deficiency, presenting as amenorrhoea, infertility and atrophy of secondary sexual characteristics with loss of axillary and pubic hair and impotence or loss of libido. Puberty is delayed in children.

● Secondary adrenocortical hypofunction (ACTH deficiency) In contrast to the primary form (Addison's disease), patients are not hyperpigmented because ACTH secretion is not raised. The sodium and water deficiency and hyperkalaemia characteristic of Addison's disease do not usually occur because aldosterone secretion (which is controlled by angiotensin and not by ACTH) is normal. However, cortisol is needed for normal free water excretion, and consequently there may be a dilutional hyponatraemia due to cortisol deficiency. Cortisol is also necessary for the maintenance of normal blood pressure. Hypotension may be associated with ACTH deficiency. Cortisol and/or GH deficiency may cause increased insulin sensitivity with fasting hypoglycaemia.

● Secondary hypothyroidism (TSH deficiency) This may sometimes be clinically indistinguishable from primary hypothyroidism.

● Prolactin deficiency Associated with failure to lactate, this may occur after post-partum pituitary infarction (Sheehan's syndrome). However, in hypopituitarism due to a tumour, plasma prolactin concentrations are often raised and may cause galactorrhoea (secretion of breast fluid). Patients with hypopituitarism, like those with Addison's disease, may die because of an inability to secrete an adequate amount of cortisol in response to stress caused by, for example, infection or surgery. Other life-.threatening complications are hypoglycaemia and hypothermia

Pituitary tumours The clinical presentation of pituitary tumours depends on the type of cells involved and on the size of the tumour (microadenomas less than 10 mm and macroadenomas more than 10 mm).

Tumours of secretory cells may produce the clinical effects of excess hormone secretion:

● excess prolactin causes infertility, amenorrhoea and varying degrees of galactorrhoea

● excess GH causes acromegaly or gigantism.

● excess ACTH causes Cushing's syndrome

Investigation of suspected hypopituitarism The laboratory should always be consulted before any complex investigation or uncommon test is performed, in order to check the details of specimen collection and handling. Defi ciency of pituitary hormones causes hypofunction of the target endocrine glands. Investigation aims to confi rm such defi ciency, to exclude disease of the target gland and then to test pituitary hormone secretion after maximal stimulation of the gland. Measurement should be made of the plasma concentrations of: ● LH, FSH and oestradiol (female) or testosterone (male), ● total or free T4 and TSH, ● prolactin, to test for hypothalamic or pituitary stalk involvement, ● cortisol at 09.00 h, to assess the risk of adrenocortical insufficiency during later testing

Case

A 17-year-old woman presented to the endocrine clinic because of headaches, weakness and amenorrhoea. The following baseline biochemical endocrine test results were obtained. Plasma Luteinizing hormone 0.46 mU/L (1–25) Follicle-stimulating hormone 0.87 mU/L (1–15) 09.00 h cortisol 56 nmol/L (180–720) Prolactin 460 mU/L (<470) Thyroid-stimulating hormone (TSH) 0.21 mU/L (0.20–5.0) Free thyroxine (T4) 10.4 pmol/L (12–25) Oestradiol 60 pmol/L (70–880) DISCUSSION The patient has panhypopituitarism. Note the low concentrations of plasma gonadotrophins and secondary hypogonadism. A low plasma cortisol concentration at 09.00 h implies also low adrenocorticotrophic hormone (ACTH) concentration. The panhypopituitarism was subsequently found to be due to a craniopharyngioma that had infiltrated the pituitary gland. Note that this case illustrates another important principle of endocrine testing: that the plasma free T4 concentration is low but the TSH concentration is within .the reference range, which is abnormal given the hypothyroxinaemia

About Adrenal Gland Disorders

The adrenal glands, located on the top of each kidney, are responsible for releasing different hormones. Adrenal gland disorders occur when the adrenal glands produce too much or too little of these hormones.

What are the adrenal glands?

The adrenal glands, located on the top of each kidney, are responsible for releasing different classes of hormones.

The outer part of the gland, called the adrenal cortex, produces the hormones cortisol and aldosterone. The inner part of the gland, called the adrenal medulla, produces the hormones adrenaline and noradrenaline.

These hormones—cortisol, aldosterone, adrenaline, and noradrenaline—control many important functions in the body, including[1]:

- Maintaining metabolic processes, such as managing blood sugar levels and regulating inflammation
- Regulating the balance of salt and water
- Controlling the "fight or flight" response to stress
- Maintaining pregnancy
- Initiating and controlling sexual maturation during childhood and puberty

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The adrenal glands are also an important source of sex steroids, such as estrogen and testosterone. What are adrenal gland disorders?

Adrenal gland disorders occur when the adrenal glands do not work properly. They can be classified into disorders that occur when too much hormone is produced or when too little hormone is produced.

These disorders can occur if there is a problem with the adrenal gland itself, such as a disease, genetic mutation, tumor, or infection. Or, sometimes the disorder results from a problem in another gland, such as the pituitary, which helps to regulate the adrenal gland. In addition, some medications can cause problems with how the adrenal glands function. When the adrenal glands produce too little or too many hormones, or when too many hormones come into the body from an outside source, serious health problems can develop.
Overall, adrenal gland disorders are generally rare. The number of people affected and at risk depends on the specific type of adrenal gland disorder

What are some types of adrenal gland disorders?

There are several types of adrenal gland disorders, each with its own symptoms and treatments.

Adrenal Gland Tumors

Most adrenal gland tumors—abnormal growths on the adrenal glands—are not cancerous. They often do not cause symptoms or require treatment. However, adrenal gland tumors can produce a variety of different hormones, leading hormone levels to get too high.

Adrenal tumors can cause:

- Cushing's syndrome, by producing cortisol so that body levels get too high
- Primary hyperaldosteronism, by creating high levels of the hormone aldosterone (controls blood pressure and body salt and potassium levels)
- Pheochromocytoma, by producing too much adrenaline (regulates the "fight-or-flight" response)

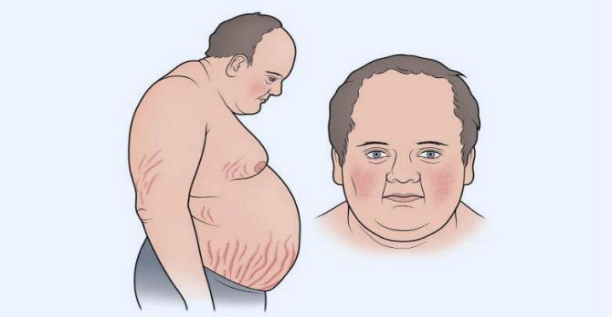
Adrenocortical Carcinoma

This is a cancerous adrenal tumor that tends to develop in the outer layer of the adrenal gland. Cancerous adrenal tumors are often found years after they start growing, at which point the cancer have spread to other organs.

Cushing's Syndrome

Cushing's syndrome is a rare disease that results from having too much cortisol hormone in the body. In some cases, Cushing's syndrome develops from long-term or overuse of steroid medications(medicines that act like cortisol in the body). In other cases, the body itself produces too much cortisol. This overproduction can happen for several reasons, including the presence of tumors(abnormal growths) such as a:

- Tumor of the pituitary gland (this is called Cushing's disease)
- Tumor of the adrenal gland (as explained above)
- Tumor in another part of the body (these are called "ectopic" tumors and are more commonly found in the pancreas, lung, or the thyroid gland)



Congenital Adrenal Hyperplasia (CAH)

CAH is a common genetic disorder in which the body makes too little cortisol. People with CAH may also have other hormone imbalances. For example, their bodies might not make enough aldosterone (controls blood pressure and body salt and potassium levels), but might make too much androgen (promotes the development of male sexual organs).

Pituitary Tumors

The pituitary gland is located at the base of the brain. It releases hormones that affect many of the body's functions. Among those hormones is the adrenocorticotropic hormone (ACTH), which stimulates the adrenal glands to release the hormone cortisol.

Sometimes, benign (noncancerous) pituitary tumors or—more rarely cancerous tumors—may grow on the pituitary gland, which can cause a variety of problems. Some pituitary tumors release too much ACTH, which, in turn, can cause the adrenal glands to produce too much cortisol. Cushing's disease refers to pituitary tumors that cause Cushing's syndrome.

Pheochromocytoma

Pheochromocytomas are part of a larger family of tumors, called paragangliomas. Pheochromocytoma is a type of tumor that develops in the adrenal medulla, the inner part of the adrenal gland. It produces adrenaline, causing high levels of this hormone in the body. In most cases, the tumors are not cancerous and do not spread to other parts of the body. But in about 10% of cases, the tumors are cancerous and can spread.[5]

Adrenal Gland Suppression

The normal activity of the adrenal glands can be suppressed—or reduced—when people take steroid medications (medicines that act like cortisol in the body) such as prednisone, hydrocortisone, or dexamethasone. Steroid medications, most often prednisone, may be prescribed to treat certain types of arthritis, severe allergic reactions, asthma, autoimmune diseases, and other conditions.

Ordinarily, someone taking steroids takes gradually lower and lower doses as time goes by until they stop taking the drug completely. This is called "tapering" the dose. When steroid medications are stopped suddenly, especially after being taken for

several weeks or more, the adrenal glands may be unable to produce steroid hormones (most importantly, cortisol) in sufficient amounts for several weeks or even months. This situation can cause health problems because of the imbalance of hormone levels that continues until the adrenal glands start functioning normally again.

Addison's Disease

This rare disorder develops when the adrenal glands do not make enough cortisol. In most cases of Addison's disease, the body also doesn't make enough of the hormone aldosterone.

Addison's is an autoimmune disease—a condition in which the immune system, which is supposed to protect the body, mistakenly attacks the body's own tissues and cells. In the case of Addison's disease, this reaction results in damage to the adrenal glands. In the long term, this damage can get worse until eventually the adrenal glands aren't working at all.

Hyperaldosteronism

This disorder occurs when the body produces too much aldosterone, a hormone that controls blood pressure and regulates the body's salt and potassium levels. The extra aldosterone is produced either by a tumor, which typically affects one adrenal gland, or by abnormal growth of both glands, a condition called "hyperplasia."