Pituitary Gland Embryology, Anatomy and Physiology

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The pituitary gland, also known as the hypophysis cerebri, is a small protrusion at the base of the brain largely encased by the sphenoid bone. Together with the immediately adjacent hypothalamus the pituitary forms the hypothalamic-pituitary system that is the body's main regulator of hormone production and is therefore intimately involved in human growth, development, reproduction, parturition, lactation, metabolism, response to stress and osmotic balance.

The pituitary gland consists of two distinct parts, the anterior pituitary, or adenohypophysis, and the posterior pituitary, or neurohypophysis. The two parts differ in origin, structure and function. The anterior pituitary derives from the oral ectoderm and produces growth hormone, prolactin, adrenocorticotropic hormone (ACTH), melanocyte-stimulating hormone (MSH), thyroid-stimulating hormone (TSH), and the gonadotrophins—follicle-stimulating hormone (FSH) and luteinising hormone (LH). The posterior pituitary originates from the neural ectoderm and consists of neurons projecting from the hypothalamus that produce antidiuretic hormone and oxytocin.

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Anatomy of the Pituitary Gland

The pituitary gland is a red-grey ovoid structure that protrudes from the base of the brain. In adults it is roughly 12 mm in the transverse diameter and 8 mm in anterior-posterior diameter and it usually weighs from 500 to 1000 mg. The pituitary gland is comprised of two distinct regions or lobes, the anterior pituitary, or adenohypophysis, and the posterior pituitary, or neurohypophysis.

The pituitary lies within the *sella turcica,* the hypophyseal fossa of the sphenoid bone, which is located in the centre of the skull base [1] (Fig. 32.1a and c). The location of the pituitary gland within this fossa of the sphenoid bone permits the most common surgical approach to the pituitary to be transphenoidal. The transphenoidal approach is easier in adults than children because of the greater pneumatisation of the sphenoid bone [2] (Fig. 32.1a–d).

The pituitary gland is covered superiorly and largely separated from the brain by a circular fold of dura mater known as the diaphragmatic *sella*. The diaphragmatic sella has a central opening, or aperture, for the infundibular stalk, which connects the pituitary to the brain. Anteriorly, the diaphragmatic sella separates the anterior part of the pituitary from the optic chiasm, which lies roughly 10 mm above the diaphragmatic sella

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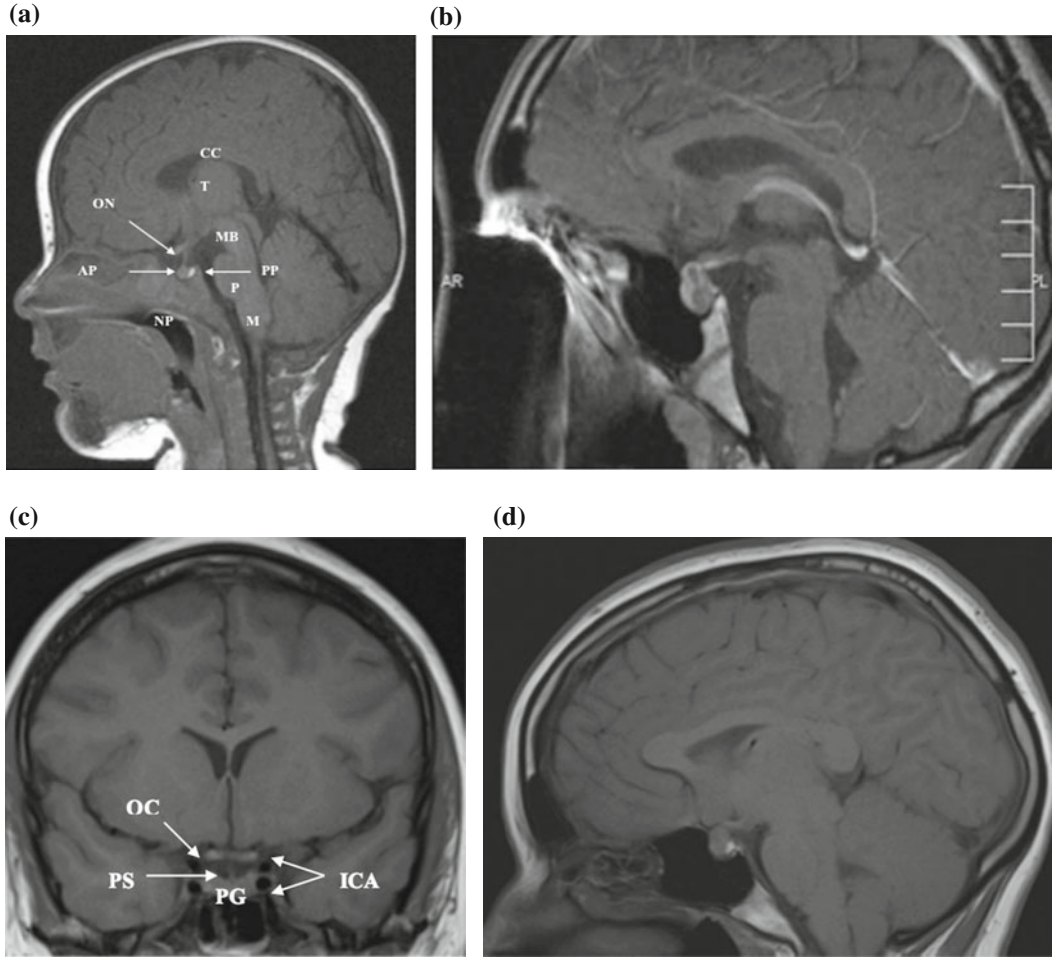

Fig. 32.1 **a** Midline sagittal section of brain MRI depicting the gross anatomical relations of anterior pituitary in a 2.5 year old infant. **b** Midline sagittal section of brain MRI in an adolescent male with Rathke's pouch cyst abutting the optic chiasm. **c** Coronal section of brain MRI at the level of pituitary. **d** Midline sagittal section of brain MRI in an adolescent female with enlarged pituitary gland. The gland appears to be moulding the optic chiasm. Follow-up MRI after 4 months showed resolution of the enlargement. This type of enlargement is not uncommon during adolescence. Sphenoid sinus is fully developed in this age rendering transphenoidal approach easier. *AP* anterior pituitary; *CC* corpus callosum; *ICA* internal carotid artery; *M* Medulla oblongata; *MB* midbrain; *NP* nasopharynx; *OC* optic chiasm; *ON* optic nerve; *P* pons; *PG* pituitary gland; *PP* posterior pituitary; *PS* pituitary stalk; *S* sphenoid sinus; *T* thalamus

[3]. The proximity of the pituitary to the optic chiasm accounts for the visual field loss that is often associated with large pituitary tumours.

When viewed from above the diaphragmatic sella may be concave, flat or convex and ranges in width from 5 to 11 mm in adults. The aperture of the sella varies in size and, if wide enough, can result in herniation of the arachnoid mater, or membrane, into the sella turcica. This herniation of the arachnoid membrane into the sella turcica enlarges the chiasmatic cistern, the subarachnoid space below the optic chiasm, and flattens the pituitary. This condition is known as the *empty sella* [4]. Herniation of the arachnoid membrane

into the sella turcica increases the risk of injury to the membrane during pituitary surgery and subsequent cerebrospinal fluid (CSF) leak [2].

The walls of the sella turcica are formed by the folds of dura mater, which also form the medial walls of the cavernous sinuses, the space lateral to pituitary filled with thin walled veins [2]. The oculomotor, trochlear and the first two branches of the trigeminal nerve run in the lateral walls of the cavernous sinuses and the abducens nerve, a portion of the internal carotid artery and the sympathetic plexus are contained within the sinuses [2]. The pituitary gland is separated inferiorly from the floor of the sella turcica by a venous sinus that communicates with the circular sinus, the veins in the spaces anterior and posterior to the sella turcica that connect the two lateral cavernous sinuses [1].

Anterior Pituitary

The anterior pituitary consists of epithelial cells that derive from the oral ectoderm [5]. It consists of the *pars anterior* (or *pars distalis*), which is the anterior or distal part of the anterior pituitary, the pars *intermedia* which is the intermediate part of the pituitary between the anterior and posterior pituitary, and *pars tuberalis* which surrounds the infundibular stem of the posterior pituitary. The pars anterior and intermedia are separated by a cleft, which is a remnant of Rathke's pouch from which the anterior pituitary develops (see section on Embryology). Pathologic enlargement of the cleft may lead to a cyst known as a Rathke's cleft cyst (Fig. 32.1b). In humans, in contrast to the mouse, the *pars intermedia* largely disappears during embryogenesis and is rudimentary and ill-defined in the adult pituitary [6]. Melanocyte-stimulating hormone (MSH) is traditionally thought to be generated in the pars intermedia; however, it may actually be produced in the pars anterior [7].

Histologically distinct cells found in the anterior pituitary include chromophil cells, chromophobe cells, and folliculostellate cells. Folliculostellate cells do not produce hormones while the chromophil and chromophobe cells produce hormones. The hormone producing cells are named for the hormone(s) they produce. The anterior pituitary produces six different peptide hormones: (1) growth hormone (GH) or somatotrophin, (2) prolactin (PRL) or mammotrophin, (3) adrenocorticotropic hormone (ACTH) or corticotrophin, (4) thyroid-stimulating hormone (TSH) or thyrotrophin, (5) follicle-stimulating hormone (FSH), and (6) luteinising hormone (LH).

The chromophobe cells comprise the majority of the cells of the anterior pituitary making up about 50% of the epithelial cells. These cells are small and do not react to routine staining. This population comprises different cell types such as degranulated secretory cells and stem cells.

The chromophil cells are either acidophils or basophils. Acidophils, also known as α-cells, include somatotrophs (producing GH), mammotrophs or lactotrophs (producing prolactin), and somatomammotrophs (producing both GH and prolactin). Basophils, also known as β-cells, include corticotrophs (producing ACTH), thyrotrophs (producing TSH), and gonadotrophs (producing LH and FSH). Pituitary tumours are often characterised as basophil or acidophil depending upon the dominant cell type. The somatotrophs are the largest and most abundant making up approximately 50% of the chromophil cells in the anterior pituitary. The thyrotroph cells make up 6–10% of the chromophil cells [8]. Corticotrophs in humans are distinguished by 300 nm secretory granules [8], and account for 10% of the chromophil cells. Gonadotrophs make up another 10–15% of the chromophil cells. They are located throughout the anterior pituitary, often in close proximity to mammotrophs [6]. The majority of gonadotroph cells have granules of 200 nm but often larger—500 nm—granules are seen. All cells that produce glycoproteins (thyrotrophs and gonadotrophs) stain PAS (periodic acid-Schiff) positive [8].

The folliculostellate cells constitute the supporting and trophic network of the hormone producing cells and contain peptides with growth factor or cytokine activity. Basic fibroblast growth factor is produced in folliculostellate cells and is implicated in the control of the production of pituitary hormones in a paracrine manner.

Posterior Pituitary

The posterior pituitary arises from the diencephalon (the posterior forebrain located between the midbrain and the cerebrum) and consists primarily of axons from supraoptic and paraventricular nuclei of the hypothalamus. These neurons secrete vasopressin (or antidiuretic hormone, ADH) and oxytocin. The posterior pituitary includes the median eminence at the base of the infundibular stalk, the infundibular stalk (or infundibulum, or stalk) and the *pars posterior* (or posterior lobe, or neural lobe). The infundibulum of the pituitary is a conical process originating from the tuber cinereum of the hypothalamus that connects the posterior pituitary to brain. In the infundibulum the thin non-myelinated axons are ensheathed by typical astrocytes [1]. As the axons continue into the posterior lobe, the astrocytes are replaced by pituicytes, which are dendritic in origin.

Blood Supply of the Pituitary

The pituitary gland receives arterial supply by a single inferior and several superior hypophyseal arteries, which arise from the internal carotid artery. Branches of these arteries supply the posterior pituitary directly and supply the anterior pituitary indirectly via the hypophyseal portal venous system [1].

The inferior hypophyseal artery originates from the cavernous part of the internal carotid artery and divides into medial and lateral branches. These branches anastomose and form a ring around the infundibulum. Branches from this circular anastomosis enter the posterior lobe to supply its capillary bed [1]. The median eminence and the upper part of the infundibulum receive an arterial supply from the superior hypophyseal arteries which arise from the supraclinoid part of the internal carotid artery and the anterior and posterior cerebral arteries [1]. The lower part of the infundibulum and pars posterior receives its supply directly from the inferior hypophyseal artery and indirectly from the superior hypophyseal artery via the trabecular arteries [1].

The hypophyseal portal system that supplies the anterior lobe consists of long and short portal vessels. The long vessels arise from the external capillary plexus and the posterior part of the internal capillary plexus of the median eminence. The two plexi form a continuum with the infundibular capillary plexus which drains into the long portal veins [1]. The long portal veins allow secretions from the median eminence to reach the anterior pituitary directly. The short portal vessels come from the capillary net of the lower infundibulum. The portal system is essential for the endocrine function of the anterior pituitary, since hormone releasing and inhibiting factors secreted from the hypothalamic nuclei collect in the median eminence and infundibulum and are transferred directly to the anterior pituitary without the dilution and metabolism that would occur if they were transported via systemic venous drainage to the heart and arterial supply back to the anterior pituitary.

The venous drainage of the anterior pituitary is restricted and only a few efferent vessels connect directly to the systemic veins of the cavernous sinuses. Venous drainage of the posterior pituitary is via the inferior hypophyseal vein to the dural sinuses, via the long and short portal veins to the anterior pituitary, and via capillaries passing through the median eminence to the hypothalamus.

Embryology of the Pituitary

Studies in different species have demonstrated that pituitary development is highly conserved from lower vertebrates through to higher mammals [9]. The mature pituitary gland has a dual embryonic origin—the anterior and intermediate lobes of the pituitary derive from the oral ectoderm, while the posterior pituitary derives from the neural ectoderm.

The pituitary or adenohypophyseal placode originates from the midline of the anterior neural ridge which is the most anterior part of the neural plate in the embryo and forms the boundary between the anterior part of the ectoderm and the neuroectoderm [10]. The pituitary placode is

immediately adjacent to the neural plate cells that give rise to the telencephalon, hypothalamus and posterior pituitary.

The pituitary placode is the site of an invagination of the oral ectoderm called *Rathke's pouch* which will give rise to the anterior and intermediate lobes of the pituitary (Fig. 32.2). In humans, the oral ectoderm containing the pituitary placode is formed by the third week of gestation. A week later Rathke's pouch begins to develop and by the end of the sixth gestational week the initial invagination completely disconnects from the oral ectoderm.

Pituitary development has been extensively studied in mice and the detailed description that follows refers to this species. Anterior pituitary development occurs in four stages: (1) formation of the pituitary placode, (2) development of a rudimentary Rathke's pouch, (3) formation of the definitive Rathke's pouch, and (4) terminal differentiation of various cell types [9].

At 7.5 dpc, the pituitary placode develops as a thickening of the ectoderm at the roof of the primitive oral cavity. The pituitary placode makes contact with the floor of the ventral diencephalon and this is a critical event in the development of the pituitary. At approximately 9 dpc, the oral ectoderm invaginates to form a rudimentary Rathke's pouch, the primordium of the anterior pituitary while the ventral diencephalon evaginates to form the infundibulum and the posterior pituitary (Fig. 32.2). Subsequently, the definitive Rathke's pouch is formed and the spatial and temporal differentiation of the various cell types within the mature anterior pituitary gland takes place [11]. At approximately 12.5 dpc, differentiated corticotrophs appear in the ventral region of the pouch and thyrotrophs on 13.5 dpc. Differentiated melanotrophs appear in the intermediate lobe a day later, and somatotroph, lactotroph and gonadotroph cells arise temporally between 15.5 and 16 days. By 17.5 dpc all hormone-secreting cell types have undergone terminal differentiation and are organised into distinct spatial networks within the gland [11].

The juxtaposition of the oral ectoderm forming Rathke's pouch and the neural ectoderm of the diencephalon which later develops into the hypothalamus is maintained in the early stages of pituitary organogenesis [11]. Inductive tissue interactions resulting from this contact and

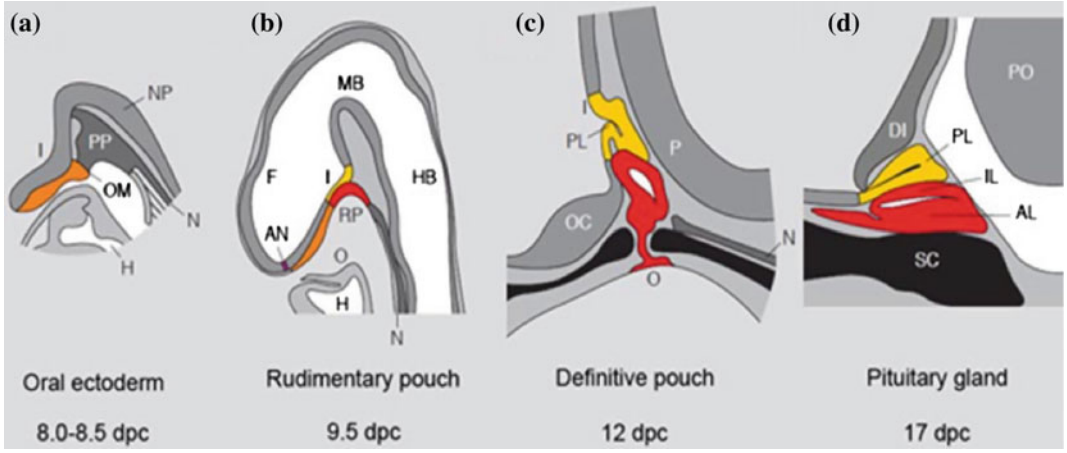

Fig. 32.2 Mouse pituitary development in sagittal section. Stages of development are indicated in dpc. *AL* Anterior lobe, *AN* anterior neural pore, *DI* diencephalon, *F* forebrain, *H* heart, *HB* hindbrain, *I* infundibulum, *IL* intermediate lobe, *MB* midbrain, *N* notochord, *NP* neural plate, *O* oral cavity, *OC* optic chiasm, *OM* oral membrane, *P* pontine flexure, *PL* posterior lobe, *P* pons, *PP* prechordal plate, *RP* Rathke's pouch, *SC* sphenoid cartilage. Adapted from Sheng and Westphal [21], with permission from Elsevier

extrinsic signalling from the neuroectoderm of the infundibulum are critical for the initial development of the pituitary gland [12]. A cascade of signalling molecules and transcription factors play crucial roles in organ commitment, cell proliferation, cell patterning and terminal differentiation events within the developing pituitary.

HESX1, PROP1, POUIF1/PIT1, LHX3, LHX4, TBX19 (TPIT), PITX1, PITX2, SF1, SOX3 and SOX2 are transcription factors implicated in pituitary organogenesis (Fig. 32.3) and mutations in these factors in humans are associated with septo-optic dysplasia, combined pituitary hormone deficiency, isolated growth hormone deficiency, or isolated adrenocorticotropic hormone deficiency (Table 32.1). This is not an exhaustive list and the roles of other transcription factors are being defined. Transcription factors act as activators or repressors and play a significant role in the cell type specification and cell fate within the pituitary gland.

Signalling molecules implicated in pituitary development are either intrinsic, emanating from the oral ectoderm such as sonic hedgehog (Shh), or extrinsic from the neuroectoderm such as Fibroblast growth factors (FGFs) and bone morphogenetic factors (BMPs) [5] (Fig. 32.3).

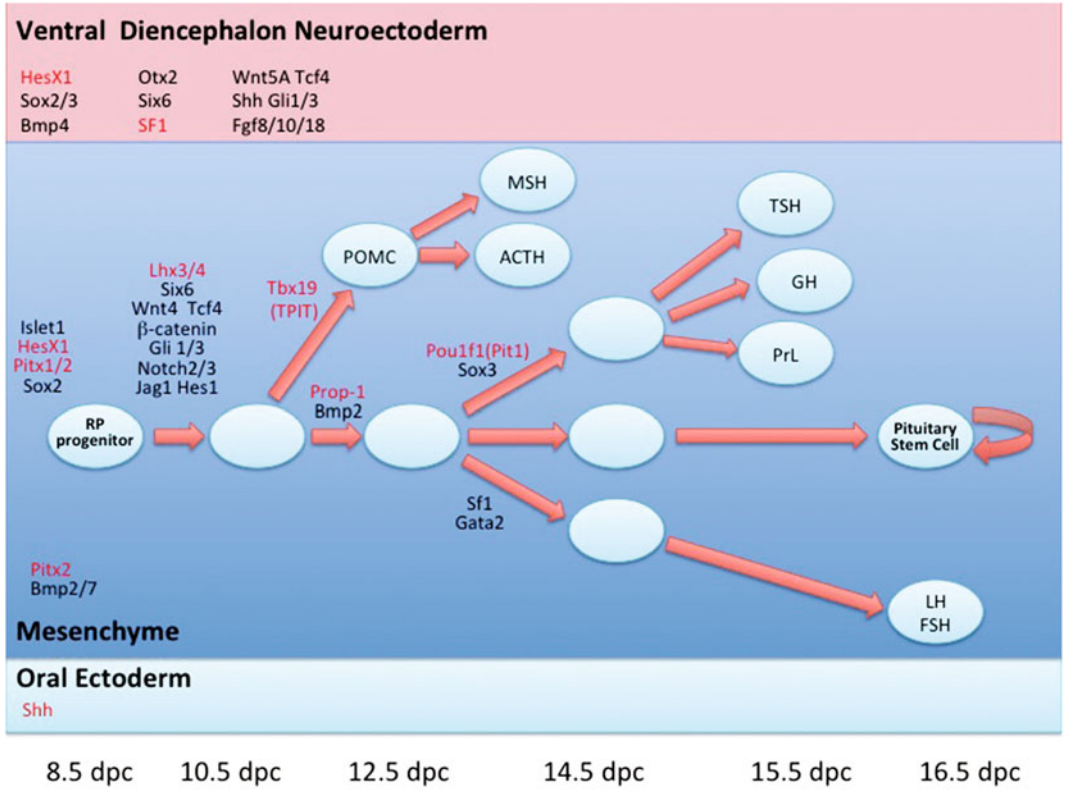

Fig. 32.3 Schematic representation of the developmental cascade of genes implicated in human pituitary development with particular reference to pituitary cell differentiation. From Kelberman et al. [5], with permission from The Endocrine Society

Table 32.1 Transcription factors and signalling molecules implicated in pituitary abnormalities and associated phenotypes

Gene	Phenotype	Inheritance
HESX1	Variable: SOD, CPHD, IGHD with EPP. APH or absent; PP: ectopic or eutopic	AD or AR
OTX2	Anophthalmia, APH, EPP, absent infundibulum	Het: haploinsufficiency
SOX2	Bilateral anophthalmia/microphthalmia, IHH, APH, Hypothalamic hamartoma, abnormal CC, Esophageal atresia, SNHL	De novo haploinsufficiency
SOX3	IGHD with LD, CPHD, APH, infundibular hypoplasia, persistent craniopharyngeal canal, EPP, midline abnormalities	X-linked recessive
GLI2	HPE, CPHD, craniofacial abnormalities, polydactyly	Haploinsufficiency
LHX3	CPHD, short rigid cervical spine, SNHL, APH or enlarged AP	AR
LHX4	CPHD, persistent craniopharyngeal canal, abnormal cerebellar tonsils, APH, EPP, absent infundibulum	AR; AD; haploinsufficiency
PROP1	CPHD, enlarged pituitary with later involution	AR
POU1F1 (*PIT1*)	CPHD, APH	AD or AR
TBX19/ *TPIT*	Isolated ACTHD	AR
SHH	HPE, cleft lip/palate	AD
FGF8	Variable: IHH, KS, cleft lip/palate, HPE	AD or AR
ARNT2	CPHD – ACTH, TSH and GHD with DI, CAKUT, progressive microcephaly with LD	AR

ACTHD ACTH deficiency, *APH* anterior pituitary hypoplasia, *CAKUT* Congenital abnormalities of the kidney and urinary tract, *CPHD* combined pituitary hormone deficiencies, *EPP* ectopic posterior pituitary, *HPE* holoprosencephaly, *IGHD* isolated GH deficiency, *IHH* isolated hypogonadotrophic hypogonadism, *KS* Kallmann syndrome, *LD* learning difficulties, *PP* posterior pituitary, *SNHL* sensorineural hearing loss, *SOD* septo-optic dysplasia
Features described here are not always present but have been variably described

These molecules may activate or repress transcription factors such as Hesx1, Lhx3 and Lhx4. They may also act as morphogens and create the appropriate environment for cell differentiation thus playing a critical role in cell fate. Such signalling molecules include members of the Shh family, FGFs, transforming growth factors (Tgfs), Bmps, Wingless (Wnts) and molecules in the Notch pathway to mention a few. To date, not many pituitary phenotypes have been reported in association with mutations in these signalling molecules (Table 32.1). However it appears that they may be implicated in pituitary tumorigenesis such as in the case of the Wnt signalling pathway [13]. A number of microarray studies have identified altered expression of Wnt inhibitors in pituitary tumours and there is clear evidence that the Wnt/β catenin pathway is involved in the pathogenesis of craniopharyngioma, a rare tumour in the hypothalamic-pituitary region.

Physiology of the Pituitary

The hypothalamic-pituitary system is the central regulator of hormone production in the body. The anterior pituitary secretes the following hormones:

(i) growth hormone (GH) or somatotropin
(ii) prolactin (PRL)
(iii) adrenocorticotropic hormone (ACTH) or corticotrophin
(iv) melanocyte-stimulating hormone (MSH) which is also produced by the intermediate lobe

(v) thyroid-stimulating hormone (TSH) or thyrotrophin
(vi) gonadotrophins: follicle-stimulating hormone (FSH) and luteinising hormone (LH)

GH and PRL are single peptides, ACTH and MSH are peptides deriving from a single precursor and TSH and the gonadotrophins are glycoproteins composed of a common α-peptide chain (89 residues) and a variable β-peptide chain.

The posterior pituitary gland secretes vasopressin or antidiuretic hormone (ADH) or AVP (arginine–vasopressin) and oxytocin. The synthesis of ADH and oxytocin takes place in the supraoptic and paraventricular hypothalamic nuclei. ADH and oxytocin reach the posterior pituitary lobe via axons of the hypothalamic neurons which project to the posterior pituitary and are secreted in the capillaries in response to hypothalamic stimuli. ADH and oxytocin share a high degree of sequence homology. ADH is activated by hyperosmolar stimuli and acts on the collecting ducts of the kidneys to facilitate water reabsorption. Oxytocin is produced at the late stage of labour both in the mother and in the baby resulting in smooth muscle contraction in the uterus and in the mammary gland.

The production of anterior pituitary hormones is regulated by a cascade system that is characterised by signal amplification and negative feedback inhibition [14]. The negative feedback systems operate when sufficient amounts of the ultimate hormone have been reached in the circulation. There are three negative feedback systems (1) long feedback; i.e. the ultimate hormone produced in the periphery back to the pituitary or brain, (2) short feedback; i.e. the anterior pituitary hormone back to the hypothalamus, and (3) ultra-short feedback; i.e. the hypothalamic releasing factor back to the hypothalamus [14].

Puberty (Fig. 32.1d) and pregnancy are two periods in human lifespan characterised by physiological enlargement of the pituitary, presumably because of the increased activity of the gland [15]. In childhood, conditions characterised by abnormal secretion of pituitary hormones are usually congenital deficiencies/insufficiencies (Table 32.2).

Growth Hormone (GH)

GH is a 22 kda peptide of 191 amino acid residues secreted by somatotroph cells. Its main effects are promotion of *growth* and *metabolism*. GH is an *anabolic hormone* promoting protein synthesis and an important *counter-regulatory hormone to hypoglycaemia*. The last action is mediated via the increase in plasma glucose concentration (diabetogenic action) and the release of free fatty acids that can serve as an alternative energy source.

The promotion of *growth* is largely mediated via GH stimulation of the liver production of Insulin-like growth factor (IGF) 1. IGF-1 acts on bone growth plates to promote linear growth. GH also has some direct action on the growth plate. Clinically, it is useful to measure IGF-1 as a surrogate marker of GH secretion or GH replacement for individuals on GH treatment.

GH is secreted in the pituitary gland following stimulation by GH-releasing hormone (GHRH) from the hypothalamus. GH production is inhibited by the hypothalamic peptide somatostatin. GH is normally secreted in a pulsatile manner. Peak levels of GH coincide with peak levels of GHRH. Trough levels of GH coincide with peak levels of somatostatin. In childhood, GH is secreted in a circadian pattern with GH peaks occurring every 1–2 h. Insufficiency of GH production is usually diagnosed using GH stimulation tests that include insulin tolerance test, glucagon provocation, exercise, dopamine, etc. However, the diagnosis of GH insufficiency is challenging as no test is perfect and the diagnosis is therefore based upon a combination of auxological (or growth), biochemical and neuroradiological data.

Table 32.2 Conditions with abnormal secretion of pituitary hormones

Hormone	Secretion	Causes
ACTH	Insufficiency	Congenital Isolated ACTHD (*TBX19/TPIT* mutations), CPHD, may be evolving (*PROP1* mutations) Acquired: tumour, surgery, trauma, radiotherapy, infiltration, autoimmune, post-infectious
	Excess	Cushing disease
TSH	Insufficiency	Congenital: Isolated (*TRHR* mutations, *TSHβ* mutations, *IGSF1* mutations), CPHD Acquired: tumour, surgery, trauma, radiotherapy, infiltration, autoimmune, post-infectious
Gonadotrophins	Insufficiency	Congenital: HH (mutations in *GPR54, GnRHR*), KS (mutations in *FGFR1, FGF8, KAL1, PROK2, PROKR2, CHD7, WDR11, NELF*); congenital forms may rarely present in adulthood Acquired: tumour, surgery, trauma, radiotherapy, infiltration, autoimmune, post-infectious
GH	Insufficiency	Congenital: IGHD (*GHRH-R*, *GH1* mutations), CPHD Acquired: tumour, surgery, trauma, radiotherapy, infiltration, autoimmune, post-infectious
	Excess	Adenoma: gigantism in childhood, acromegaly in adulthood
PRL	Excess	Prolactinoma
ADH	Insufficiency	Congenital: Isolated or CPHD Acquired: tumour, surgery, trauma, radiotherapy, infiltration, autoimmune, post-infectious
	Excess	SIADH –(transient) either from pituitary secretion of ADH or from ectopic production
Oxytocin	Insufficiency	CPHD, unknown clinical significance outside parturition/lactation

CPHD combined pituitary hormone deficiencies, *IGHD* isolated GH deficiency, *HH* Hypogonadotrophic Hypogonadism, *KS* Kallmann syndrome, *SIADH* syndrome of inappropriate antidiuretic hormone

Prolactin (PRL)

Prolactin is a peptide of 198 amino acid residues produced by lactotroph cells. It has considerable structural homology to GH. The classic endocrine action of this hormone is the promotion of growth and maturation of the mammary gland during pregnancy in order to achieve lactation. The exact mechanism of the mammotrophic effect of PRL in humans is largely unknown and our knowledge is based on animal studies.

Apart from its classic endocrine action, PRL has other autocrine–paracrine actions as a growth factor, neurotransmitter, and immunoregulator [16]. In males of most animal species, PRL stimulates testicular function [16]. Other actions ascribed to PRL include effects on metabolism, salt and water balance, sexual function and reproduction, and brain and behaviour.

The mechanism of PRL secretion is largely unknown and it is thought to be under the influence of a PRL-releasing factor that is not well defined and a PRL-inhibiting factor, also not well defined but it may be dopamine or a peptide controlled by dopamine [14]. Additionally, hypothalamic thyrotrophin releasing hormone (TRH) may stimulate PRL production.

Adrenocorticotropic Hormone (ACTH)

ACTH is a relatively small peptide of only 39 amino acid residues which derives along with α-MSH, β-lipotropin and β-endorphin from a

single common precursor, the pre-pro-opiomelanocortin. ACTH regulates the production of glucocorticoids. Cortisol is the major glucocorticoid in humans and is released in the circulation both in a circadian and in a pulsatile manner. Circadian secretion of cortisol is subject to the circadian production of corticotrophin releasing hormone (CRH) by the hypothalamus. The highest ACTH production is at 0800 in the morning.

Glucocorticoid secretion in response to stress is crucial for homeostasis and deficiency of ACTH is life-threatening. ACTH binds to the melanocortin 2 receptors (MC2-R) which are widely distributed throughout the body [17]. Additionally, ACTH regulates the production of adrenal androgens androstenedione and dehydroepiandrosterone by the zona reticularis of the adrenal cortex. Glucocorticoids inhibit the production of ACTH in a classic model of hormonal negative feedback.

Melanocyte-Stimulating Hormone (MSH)

MSH derives from the same precursor as ACTH. Its action in humans is unclear but it may have a role in skin pigmentation. ACTH has some MSH activity that is evident by the increased skin pigmentation often seen in patients with high ACTH levels including those with Addison's disease. However, MSH does not appear to exert any ACTH-like action.

Thyroid-Stimulating Hormone (TSH)

TSH is a 28 kda glycoprotein which regulates the production of thyroxine and triiodothyronine by thyroid follicular cells [8]. TSH secretion is stimulated by hypothalamic thyrotropin-releasing hormone (TRH). There is a negative feedback mechanism with thyroxine (T4) and triiodothyronine (T3) suppressing TSH secretion. Thyroid hormones exhibit complex metabolic effects with the increased thyroid hormone concentrations in hyperthyroidism causing an increase in the basal metabolic rate, tachycardia, excess growth, sweating, poor concentration and weight loss. Low concentrations of thyroid hormone in hypothyroidism are classically associated with poor growth and short stature, weight gain, fatigue, lethargy and bradycardia. Features of hypothyroidism may be subtle in childhood.

Gonadotrophins—Follicle-Stimulating Hormone (FSH) and Luteinising Hormone (LH)

The gonadotrophins are glycoproteins consisting of α and β subunits. The β subunit confers specific biological activity and consists of 121 amino acids in LH and 118 amino acids in FSH. Gonadotrophin production is stimulated when hypothalamic gonadotrophin releasing hormone (GnRH) binds to specific receptors on the gonadotroph cells of the anterior pituitary. LH and FSH produced by the anterior pituitary bind to their receptors in the gonads stimulating steroidogenesis and gametogenesis, respectively. The synthesis of LH and FSH is dependent on the pattern of GnRH secretion such that an increased frequency of pulsatile hypothalamic GnRH release favours LH β gene transcription over FSH β gene transcription while a decreased frequency of pulsatile GnRH release, such as occurs in the luteal and early follicular phase of the female menstrual cycle, favours FSH β gene transcription [18].

Sex steroids feed back to the hypothalamus and pituitary suppressing the production of GnRH and LH and FSH, respectively, and form a classic negative feedback circuit. However, by some poorly understood mechanism, in females prior to ovulation the feedback is positive instead of negative and the result is a surge in LH resulting in ovulation [19].

Before birth, the hypothalamic–pituitary–gonadal (HPG) axis is hyperactive in a sexually dimorphic manner that is essential for the sexual differentiation of the brain [20]. This activity gradually declines over a period of 3–4 months postnatally and a long period of inactivity follows until adolescence.

Lack of gonadotrophins due to either GnRH deficiency or reduced action leads to hypogonadotrophic hypogonadism, with delayed or absent puberty and impaired fertility (Table 32.2).

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