Pathophysiology of Pituitary Gland Disorders

PHCL 415
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Learning Objectives

- Understand the physiology of pituitary gland
- Understand acromegaly & describe its clinical features
- Describe the typical clinical features of patients with growth-hormone–deficient short stature
- Discuss the different etiologies of persistent elevated serum prolactin & describe clinical features in hyperprolactinemia
- List common pharmacologic agents that can potentially induce hyperprolactinemia
- Understand other pituitary disorders including pharmacologic treatment of panhypopituitarism. SIADH & diabetes insipidus

Outline

- Introduction
- Anatomy & Physiology of Pituitary gland
- Pituitary Disorders
  - Causes/Classification
  - Pathophysiology
  - Manifestations
  - Diagnosis

Introduction

Introduction

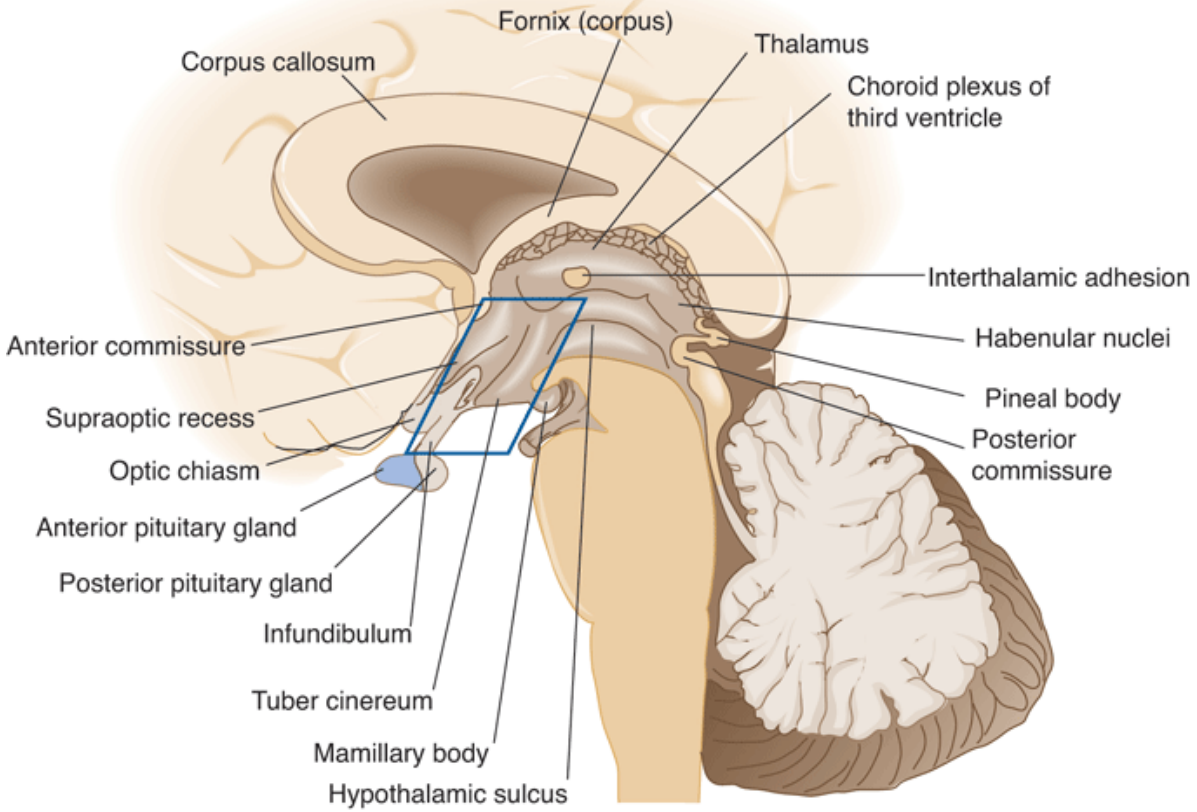
- Often referred to as the "master gland“
- The hypothalamus & the pituitary gland are closely connected, & together they provide a means of communication between the brain & many of the body's endocrine organs
- The hypothalamus uses nervous input & metabolic signals from the body to control the secretion of pituitary hormones that regulate growth, thyroid function, adrenal activity, reproduction, lactation, & fluid balance

Anatomy & Physiology

Pituitary Gland

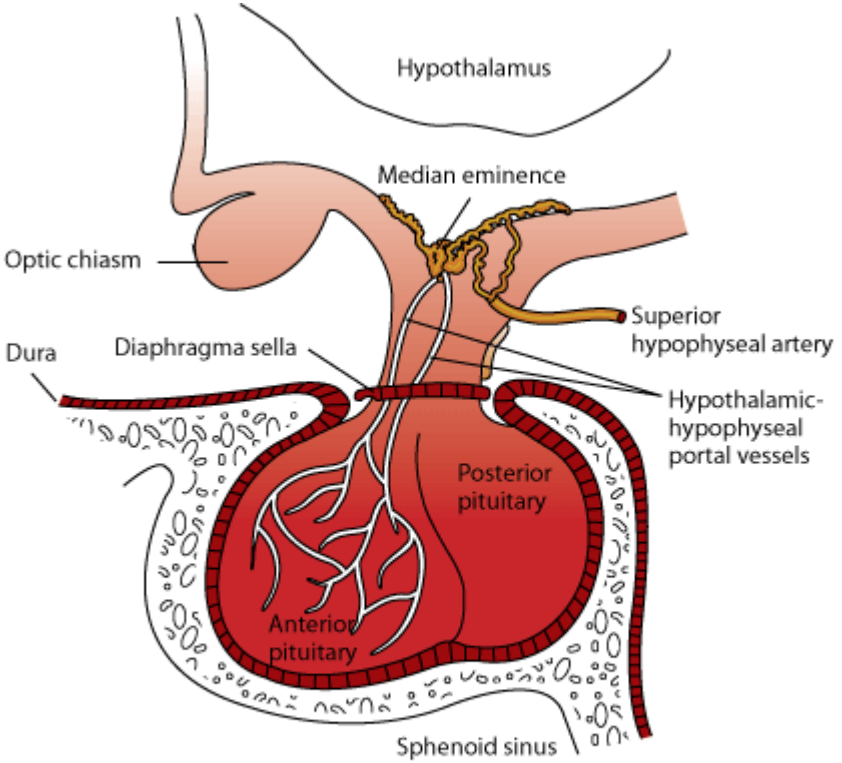
- The pituitary gland, is located at the base of the brain in a cavity of the sphenoid bone “sella turcica”
- Separated from the brain by an extension of the dura mater known as the diaphragma sella
- Very small gland, weighing between 0.4 & 1 g in adults
- Divided into 2 regions, the anterior lobe, or adenohypophysis, & the posterior lobe, or the neurohypophysis

Pituitary Gland



Source: McPhee SJ, Hammer GD: *Pathophysiology of Disease: An Introduction to Clinical Medicine, 6th Edition*: http://www.accessmedicine.com

Pituitary Gland



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Pituitary Gland

Anterior pituitary

- Growth hormone (GH)
- Gondadotrophs (LH/FSH)
- TSH
- Prolactin
- Corticotropin (ACTH)

Posterior pituitary

- Oxytocin
- Vasopressin

Pituitary Hormones

Hormone	Stimulation	Inhibition	Physiologic Effects
Anterior pituitary			
Growth hormone (GH)	***Physiologic***	***Physiologic***	
	GH-releasing hormone	Somatostatin	Stimulates IGF-I production
	Ghrelin	Elevated IGF-1	IGF-I & GH promote growth in all body tissues
	GABA	Progesterone	
	Norepinephrine	Glucocorticoids	
	Dopamine	Hyperglycemia	
	Serotonin	↑ free fatty acids	
	Estrogen		
	Sleep		
	Stress/Exercise		

Introduction

Hormone	Stimulation	Inhibition	Physiologic Effects
Anterior pituitary			
Growth hormone (GH)	***Pharmacological***	***Pharmacological***	
	Adrenergic agonists (e.g., clonidine)	Dopamine antagonists (e.g., phenothiazines)	
	Adrenergic antagonists (e.g., propranolol)	Adrenergic antagonists (e.g., phentolamine)	
	Dopamine agonists (e.g., bromocriptine)	Adrenergic agonists (e.g., isoproterenol)	
	GABA agonists (e.g., muscimol)	Serotonin antagonists (e.g., methysergide)	

Pituitary Hormones

Hormone	Stimulation	Inhibition	Physiologic Effects
Anterior pituitary			
Prolactin	***Physiologic***	***Physiologic***	
	TRH	Dopamine	Lactation
	VIP	GABA	
	Estrogen		
	Serotonin		
	Histamine		
	Endogenous opioids		

Pituitary Hormones

Hormone	Stimulation	Inhibition	Physiologic Effects
Anterior pituitary			
Prolactin	***Pharmacological***	***Pharmacological***	
	Dopamine antagonists (e.g., phenothiazines, haloperidol, methyldopa)	Dopamine agonists (e.g., L-dopa, bromocriptine, pergolide, cabergoline)	
	Opiates		
	Estrogens		
	H_2-antagonists (e.g., cimetidine)		

Introduction

Hormone	Stimulation	Inhibition	Physiologic Effects
Anterior pituitary			
Adrenocortic-otropic hormone (ACTH)	CRH	Elevated cortisol	Glucocorticoid effects
Thyroid-stimulating hormone (TSH)	TRH	Thyroxine	Iodine uptake & thyroid hormone synthesis
	Estrogens	Triiodothyronine	
	Norepinephrine	Somatostatin	
	Serotonin	Glucocorticoids	
	Dopamine		

Introduction

Hormone	Stimulation	Inhibition	Physiologic Effects
Anterior pituitary			
Luteinizing hormone (LH)	GnRH	Estradiol	Ovulation
		Testosterone	Maintains corpus luteum
		Fasting	
Follicle-stimulating hormone (FSH)	GnRH	Estradiol	Ovarian follicle development
	Menopause	Fasting	Stimulates estradiol & progesterone
	Ovarian disorders		

Introduction

Hormone	Stimulation	Inhibition	Physiologic Effects
Posterior pituitary			
Vasopressin (antidiuretic hormone [ADH])	Hyperosmolality	Hypervolemia	Acts on renal collecting ducts to prevent diuresis
	Volume depletion	Hypoosmolality	
Oxytocin	Parturition		Uterine contraction
	Suckling		Milk ejection

Pathophysiology of Selected pituitary disorders

Pituitary Disorders

- Disorders of hormone deficit
- Disorders of hormone excess

Pituitary Disorders

- Hypopituitarism
- Growth Hormone Excess (Acromgaly)
- Hyperprolactinemia
- Diabetes Insipidus
- Syndrome of Inappropriate Vasopressin Secretion (SIADH)

Hypopituitarism

- Panhypopituitarism
- A condition of complete or partial loss of anterior & posterior pituitary function resulting in a complex disorder characterized by multiple pituitary hormone deficiencies
- Patients with panhypopituitarism may have ACTH deficiency, gonadotropin deficiency, GH deficiency, hypothyroidism, & hyperprolactinemia

Hypopituitarism

- Panhypopituitarism can be classified as either primary or secondary depending on the etiology
- Primary panhypopituitarism involves an abnormality within the secretory cells of the pituitary
- Secondary panhypopituitarism is caused by a lack of proper external stimulation needed for normal release of pituitary hormones

Hypopituitarism

Hypothalamic-pituitary-end organ axis

	Thyroid	Adrenal	Gonads	Growth	Breast
Releasing hormone	TRH	CRH	GnRH	GHRH	Dopamine (inhibitor)
Pituitary cells	Thyrotrope	Corticotrope	Gonadotrope	Somatotrope	Lactotrope
Pituitary hormone	TSH	ACTH	LH/FSH	GH	Prolactin
End organ	Thyroid	Adrenal	Testes or ovaries	Liver	Breast gland
Product	Thyroxine	Cortisol	Testosterone or estradiol	IGF-1	Milk

Hypopituitarism

Clinical Presentation

- The complex of symptoms in hypopituitarism varies depending on the extent & duration of disease
- Regardless of the underlying cause, GH deficiency occurs as the earliest hormonal deviance, followed by ACTH & gonadotropin (LH & FSH) deficiencies, & finally, TSH deficiency
- There could be sudden or gradual loss of pituitary function

Hypopituitarism

Etiology

- Some of the most common causes of panhypopituitarism:
  - Primary pituitary tumors
  - Ischemic necrosis of the pituitary
  - Surgical trauma
  - Radiation
  - Various types of CNS infections

Hypopituitarism

Etiology

- Panhypopituitarism of sudden onset is usually due to:

➢ Traumatic disruption of the pituitary

➢ Infarction & hemorrhage into a pituitary tumor

➢ Ischemic destruction of the pituitary after systemic hypotension (eg, postpartum hypopituitarism after massive blood loss in childbirth)

Hypopituitarism

Etiology

- Gradually acquired hypopituitarism is most often due to:

➢ Extension of pituitary tumors

➢ Complication of radiation therapy for brain tumors

Hypopituitarism

Pathophysiology

- Hypopituitarism has multiple possible etiologies; the pathophysiology depends on the underlying cause
- The common endpoint is disrupted synthesis or release of one or more pituitary hormones, resulting in clinical manifestations of hypopituitarism

Hypopituitarism

Clinical Manifestations

- The symptoms & signs of hypopituitarism depend on the extent & duration of specific pituitary hormone deficiencies & the patient's overall clinical status
- Deficiency of vasopressin can be compensated for by increasing water intake
- Hypothyroidism may become manifest gradually over months because of the relatively long half-life of thyroid hormone

Hypopituitarism

Clinical Manifestations

General symptoms:

- Being chronically unfit
- Weakness and fatigue
- Loss of appetite
- Impairment of sexual function
- Cold intolerance

Acromegaly

- Acromegaly is a pathologic condition characterized by excessive production of GH
- A rare disorder that affects approximately 50 to 70 adults per million
- Gigantism, which is even more rare than acromegaly, is the excess secretion of GH prior to epiphyseal closure in children

Acromegaly

- Patients diagnosed with acromegaly are reported to have a twofold to threefold increase in mortality, usually related to cardiovascular, respiratory, or neoplastic disease
- Most patients are middle-aged at the time of diagnosis
- It does not affect one gender to a greater extent than the other

Acromegaly

- The most common cause of excess GH secretion in acromegaly is a GH-secreting pituitary adenoma, accounting for approximately 98% of all cases
- Rarely, acromegaly is caused by ectopic GH-secreting adenomas, GH cell hyperplasia, or excess GHRH secretion

Acromegaly

- Clinical signs & symptoms develop gradually over an extended period of time
- Because of the subtle & slowly developing changes in physical appearance caused by GH excess, most patients are not definitively diagnosed with acromegaly until 7 to 10 years after the presumed onset of excessive GH secretion
- Excessive secretion of GH & IGF-1 adversely affects several organ systems

Acromegaly

Clinical Manifestations
General
Patient will experience slow development of soft-tissue overgrowth affecting many body systems. Signs & symptoms gradually progress over 7-10 years
Symptoms
Patient may complain of symptoms related to local effects of the GH-secreting tumor, such as headache & visual disturbances. Other symptoms related to elevated GH and insulin-like growth factor-1 (IGF-1) concentrations include excessive sweating, neuropathies, joint pain
Signs
The patient may exhibit changes in facial features, increased hand volume, increased ring size, increased shoe size, an enlarged tongue, & various dermatologic conditions

Acromegaly

Clinical Manifestations
Laboratory tests
The patient's GH concentration will be >1 mcg/L following an oral glucose tolerance test (OGTT) & IGF-1 serum concentrations will be elevated. Glucose intolerance may be present in up to 50% of patients
Additional clinical sequelae
Cardiovascular diseases such as HTN, coronary heart disease, cardiomyopathy, & left ventricular hypertrophy
Osteoarthritis & joint damage develops in up to 90% of acromegalic patients
Respiratory disorders & sleep apnea occur in up to 60% of acromegalic patients
Type 2 diabetes develops in approximately 25% of acromegalic patients
Patients with acromegaly may have an increased risk for development of esophageal, colon, & stomach cancer

Acromegaly

Short Stature

- Short stature is a condition that is commonly defined by a physical height that is more than two standard deviations below the population mean & lower than the third percentile for height in a specific age group
- More than 1.8 million children in the United States can be characterized as having short stature
- Short stature is a very broad term describing a condition that may be the result of many different causes

Short Stature

- A true lack of GH is among the least common causes & is known as growth hormone-deficient (GHD) short stature
- Absolute GH deficiency is a congenital disorder that can result from various genetic abnormalities, such as GHRH deficiency, GH gene deletion, & developmental disorders including pituitary aplasia or hypoplasia

Short Stature

- GH insufficiency is an acquired condition that can result secondary to hypothalamic or pituitary tumors, cranial irradiation, head trauma, pituitary infarction, and various types of CNS infections

- Psychosocial deprivation, hypothyroidism, poorly controlled diabetes mellitus, treatment of precocious puberty with LH-releasing hormone agonists, & pharmacologic agents such as glucocorticoids, may induce transient GH insufficiency

Short Stature

- Short stature also occurs with several conditions that are not associated with a true GH deficiency or insufficiency
- These conditions include constitutional growth delay; malnutrition; malabsorption of nutrients associated with inflammatory bowel disease, celiac disease, & cystic fibrosis; & chronic renal failure

Short Stature

- Children with GHD short stature usually are born with an average birth weight
- Decreases in growth velocity generally become evident between the ages of 6 months & 3 years

Short Stature

Clinical Manifestations
General
The patient will have a physical height that is > 2 standard deviations below the population mean for a given age & gender
Signs
Patient will present with reduced growth velocity & delayed skeletal maturation
Children with growth hormone (GH)-deficient or GH-insufficient short stature may also present with central obesity, prominence of the forehead, and immaturity of the face
Laboratory tests
The patient will exhibit a peak GH concentration <10 mcg/L following a GH provocation test. Reduced insulin-like growth factor-1 & insulin-like growth factor-1 binding protein-3 concentrations
Because GH deficiency may be accompanied by loss of other pituitary hormones, hypoglycemia & hypothyroidism may be noted.

Hyperprolactinemia

- Hyperprolactinemia is a state of persistent serum prolactin elevation
- Hyperprolactinemia usually affects women of reproductive age
- The incidence of hyperprolactinemia in the general population is reported to be <1%

Hyperprolactinemia

- Hyperprolactinemia has several etiologies
- The most common causes are benign prolactin-secreting pituitary tumors, known as prolactinomas, & various medications
- Prolactinomas are classified according to size

Hyperprolactinemia

- Prolactin-secreting microadenomas are <10 mm in diameter & often do not increase in size
- Macroadenomas are tumors with a diameter >10 mm that continue to grow & can cause invasion of surrounding tissues

Hyperprolactinemia

Drug-Induced Hyperprolactinemia

Dopamine antagonists
Antipsychotics
Phenothiazines
Metoclopramide
Domperidone

Prolactin stimulators
Methyldopa
Selective serotonin reuptake inhibitors (SSRIs)
Estrogens
Gonadotropin-releasing hormone analogs
Benzodiazepines
Tricyclic antidepressants
H_2-Receptor antagonists
Opioids

Hyperprolactinemia

Clinical Manifestations
General
Hyperprolactinemia most commonly affects women & is very rare in men
Signs & symptoms
The patient may complain of symptoms related to local effects of the prolactin-secreting tumor, such as headache & visual disturbances, that result from tumor compression of the optic chiasm.
Female patients experience oligomenorrhea, amenorrhea, galactorrhea, infertility, decreased libido, hirsutism, & acne.
Male patients experience decreased libido, erectile dysfunction, infertility, reduced muscle mass, galactorrhea, & gynecomastia

Hyperprolactinemia

Clinical Manifestations
Laboratory tests
Prolactin serum concentrations at rest will be >20 mcg/L on multiple occasions.
Additional clinical sequelae
Prolonged suppression of estrogen in premenopausal women with hyperprolactinemia leads to decreases in bone mineral density and significant risk for development of osteoporosis.
Risk for ischemic heart disease may be increased with untreated hyperprolactinemia

Diabetes Insipidus

- Diabetes insipidus is a syndrome of polyuria
- Results from the inability to concentrate urine &, therefore, to conserve water
- This is due to lack of vasopressin action

Diabetes Insipidus

- The initial clinical presentation of diabetes insipidus is polyuria that persists in circumstances that would normally lead to diminished urine output (eg, dehydration), accompanied by thirst
- Adults may complain of frequent urination at night (nocturia), & children may present with bed-wetting (enuresis)
- No further symptoms develop if the patient is able to maintain a water intake commensurate with water loss

Diabetes Insipidus

- The volume of urine produced in the total absence of vasopressin may reach 10–20 L/d
- Thus, should the patient's ability to maintain this degree of fluid intake be compromised (eg, damage to hypothalamic thirst regulating centers), dehydration can develop & may rapidly progress to coma

Diabetes Insipidus

- Diabetes insipidus can be due to:

1. Diseases of the CNS (**central diabetes insipidus**), affecting the synthesis or secretion of vasopressin

2. Diseases of the kidney (**nephrogenic diabetes insipidus**), with loss of the kidney's ability to respond to circulating vasopressin by retaining water

3. Pregnancy, with probable increased metabolic clearance of vasopressin

Diabetes Insipidus

Causes of Central & Nephrogenic Diabetes Insipidus
Central diabetes insipidus
1. Hereditary, familial (autosomal dominant)
1. Acquired
Traumatic or postsurgical
Neoplastic disease: lymphoma, meningioma, metastatic carcinoma
Ischemic or hypoxic disorder: cardiopulmonary arrest, shock, brain death
Granulomatous disease: sarcoidosis, histiocytosis X
Infections: viral encephalitis, bacterial meningitis
Autoimmune disorder

Diabetes Insipidus

Causes of Central & Nephrogenic Diabetes Insipidus
Nephrogenic diabetes insipidus
1. Hereditary, familial (two types)
1. Acquired
Hypokalemia
Hypercalcemia
Postrenal obstruction
Drugs: lithium, demeclocycline, methoxyflurane
Sickle cell trait or disease

Diabetes Insipidus

- Signs & Symptoms:

1. Polydipsia
2. Polyuria
3. Pocturia
4. Increase serum osmolality
5. Decrease urinosmolality
6. Increase Scr & BUN

Syndrome of Inappropriate Vasopressin Secretion (SIADH)

- SIADH is due to the secretion of vasopressin in excess
- Clinical presentation of SIADH is hyponatremia without edema
- Depending on the rapidity of onset & the severity, the neurologic consequences of hyponatremia include confusion, lethargy & weakness, myoclonus, asterixis, generalized seizures, & coma

SIADH

Causes of SIADH
Tumors
CNS disorders
Mass lesions: tumors, abscess, hematoma
Infections: encephalitis, meningitis
Cerebrovascular accident
Acute psychosis
Pulmonary disorders
Infections: tuberculosis, pneumonia, abscess
Acute respiratory failure
Drugs
Vasopressin
Carbamazepine

Learning Objectives

- Understand the physiology of the human pituitary gland & the primary functions of anterior and posterior pituitary hormones
- Understand acromegaly & describe its clinical features
- Describe the typical clinical features of patients with growth-hormone–deficient short stature
- Discuss the different etiologies of persistent elevated serum prolactin & describe clinical features in hyperprolactinemia
- List common pharmacologic agents that can potentially induce hyperprolactinemia
- Understand other pituitary disorders including pharmacologic treatment of panhypopituitarism. SIADH & diabetes insipidus

References

- Pharmacotherapy: A Pathophysiologic Approach, 7e
- Pathophysiology of Disease: An Introduction to Clinical Medicine, 6e
- Applied Therapeutics: The Clinical Use of Drugs, 9e

Thank You