Congenital Hypopituitarism

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Pediatric Endocrinology

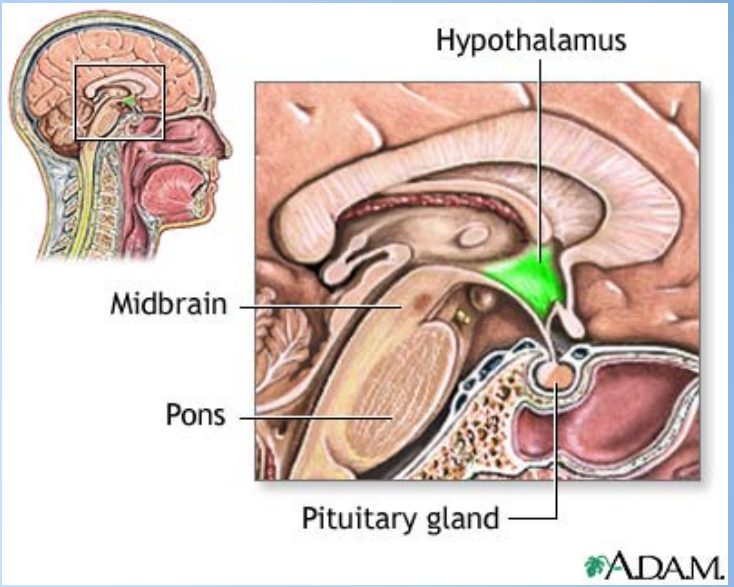
Outline

- Anatomy of the Hypothalamus and Pituitary
- Anterior Pituitary Development
- Congenital Hypopituitarism
  - Etiology
  - Presentation
  - Diagnosis
  - Treatment

Hypothalamus

Controls the release of 8 major hormones by the hypophysis and is involved in:

1. Temperature regulation
2. Control of food and water intake
3. Sexual behavior and reproduction
4. Control of daily cycles in the physiological state and behavior
5. Mediation of emotional responses



"Biological Clock"
Projection from retina to suprachiasmatic nucleus
Day-night information
Synchronizes diurnal or circadian rhythms

Hypothalamus

Consists of large number of nuclei and fiber tracts
Supraoptic and paraventricular nuclei – AVP, Oxytocin

- AVP and Oxytocin are transported down the nerve axons through infundibulum to the neurohypophysis

Arcuate Nucleus and others - releasing or inhibiting factors

- Secreted from terminals of these neurons enter portal system of vessels and carried to the adenohypophysis

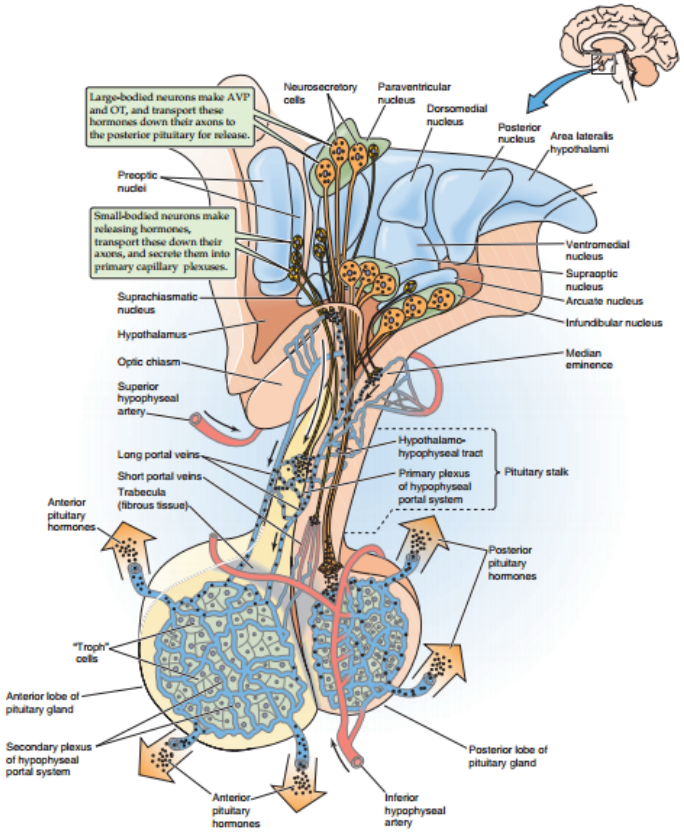


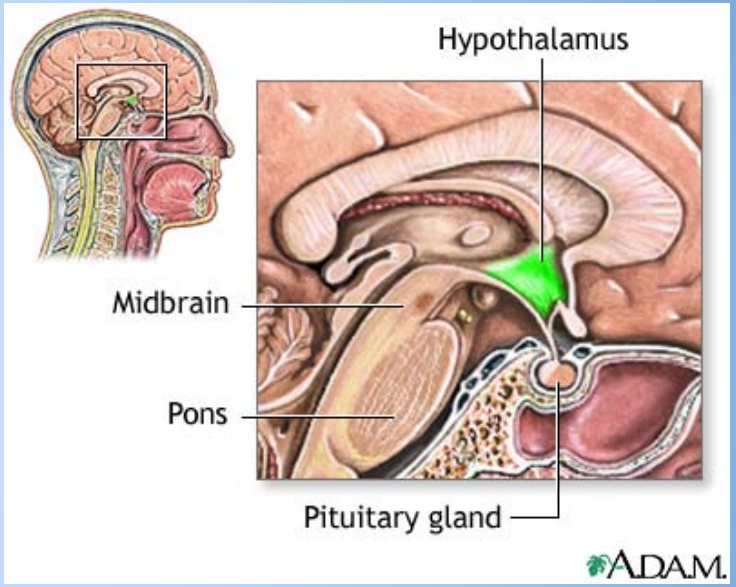
Figure 2. The hypothalamo-pituitary axis. (Boron and Boulpaep, Medical Physiology, 1st edition, Saunders 2003, Figure 46-3, page 1011.)

Hormones secreted by the hypothalamus

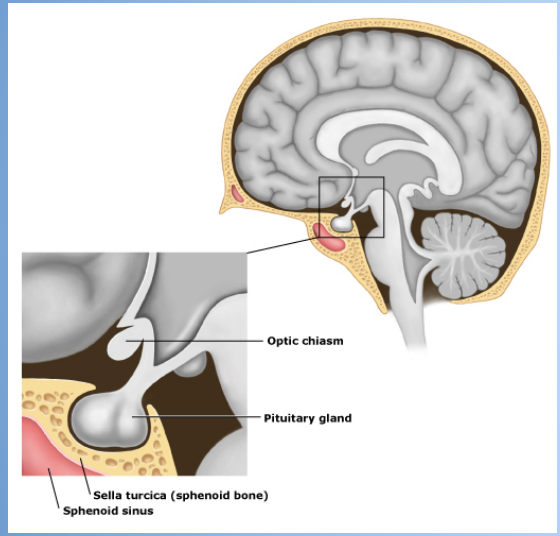
- **Anti-diuretic hormone (ADH):** increases water absorption into the blood by the kidneys
- **Corticotropin-releasing hormone (CRH):** CRH stimulates release of ACTH from anterior pituitary -> adrenal glands to release corticosteroids -> regulate metabolism and immune response
- **Gonadotropin-releasing hormone (GnRH)**: GnRH stimulates the anterior pituitary to release follicle stimulating hormone (FSH) and luteinizing hormone (LH) -> normal functioning of the ovaries and testes.
- **Growth hormone-releasing hormone (GHRH)** or **growth hormone-inhibiting hormone (GHIH)** (also known as somatostain): GHRH -> anterior pituitary release of growth hormone (GH); GHIH has the opposite effect. GH maintains healthy body composition (muscle/fat mass) and growth
- **Oxytocin**: role in orgasm, the ability to trust, body temperature, sleep cycles, and the release of breast milk.
- **Prolactin-releasing hormone (PRH)** or **prolactin-inhibiting hormone (PIH)** (also known as dopamine): PRH -> anterior pituitary to stimulate breast milk production via prolactin. PIH inhibits prolactin, and thereby, milk production
- **Thyrotropin releasing hormone (TRH):** TRH -> thyroid stimulating hormone (TSH) -> stimulates release of thyroid hormones -> regulate metabolism, energy, and growth and development

Pituitary

- Size of a pea – approx 0.5 grams
- Located - sella turcica at base of hypothalamus
- Composed of 2 functionally distinct structures
  - Adenohypophysis (anterior pituitary)
  - Neurohypophysis (posterior pituitary)
- Differ in embryologic development and anatomy

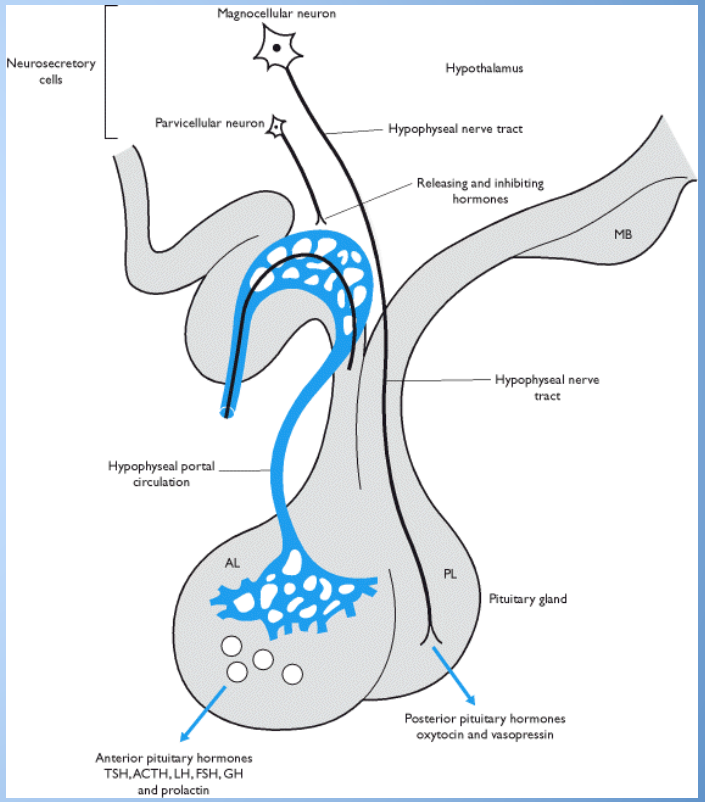


Anatomy of Pituitary



Two components:

- Adenohypophysis receives signals through portal system of blood vessels from hypothalamus and through stalk) and
- neurohypophysis (receives signal through axons that arise in neural bodies in hypothalamus and also traverse down stalk)



Central signaling integrator of
GROWTH
REPRODUCTION
HOMEOSTASIS

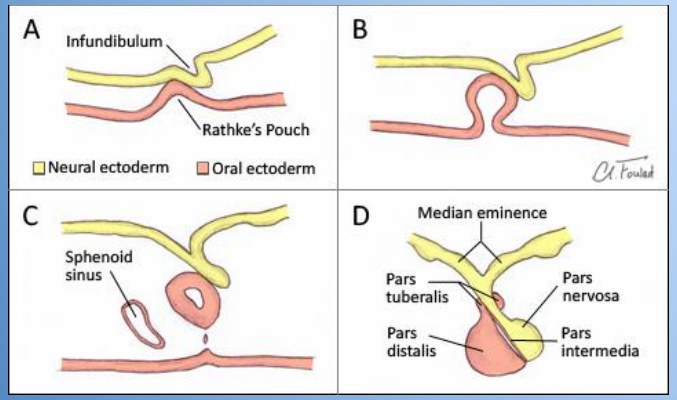
Physiology of Pituitary Development

Anterior

Up-growth of ectodermal cells from Rathke's pouch

Posterior

Down-growth of neural tissue cells from the hypothalamus



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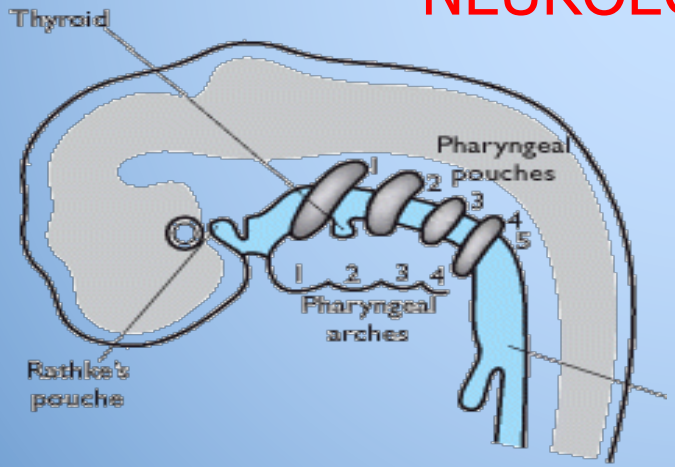
Physiology of Pituitary Development

Dual embryonic origin:

ORAL ECTODERM → Anterior & Intermediate Lobes

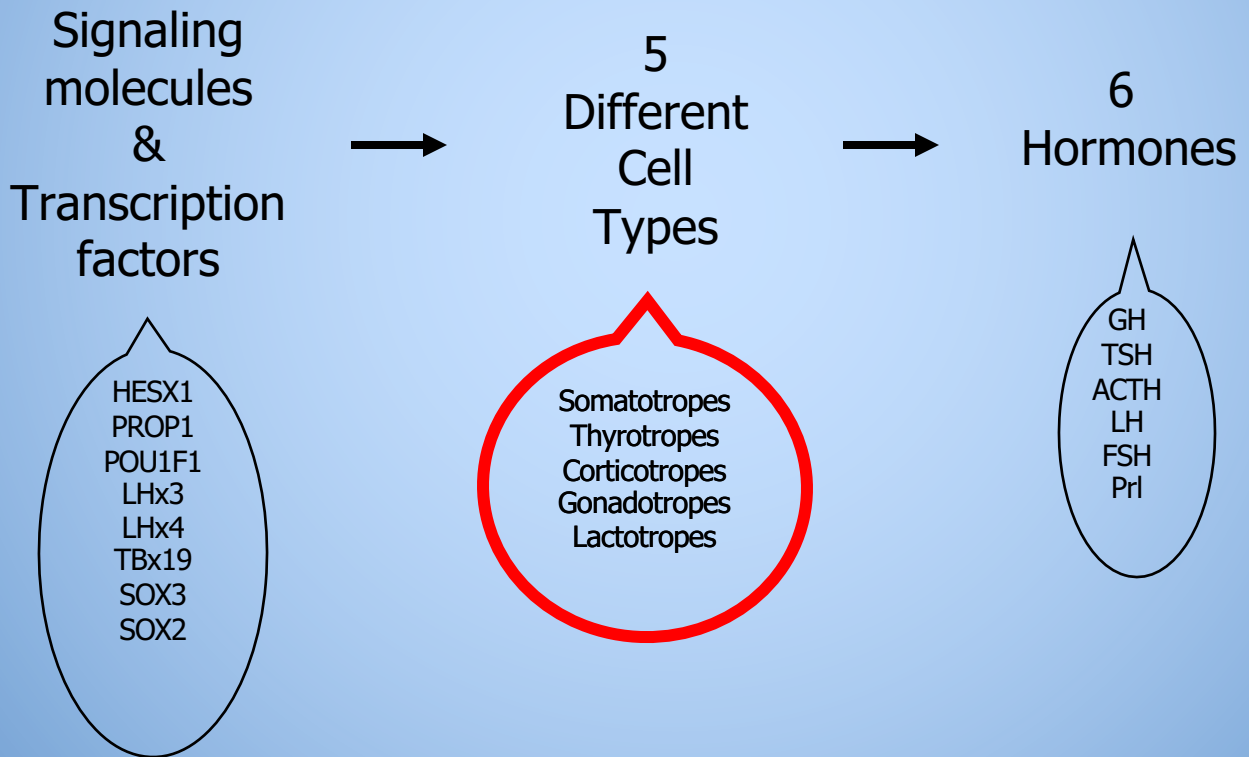
&

NEUROECTODERM → Infundibulum & Posterior Lobe



Two key concepts are TEMPORAL and SPATIAL relationships

Anterior Lobe of Pituitary



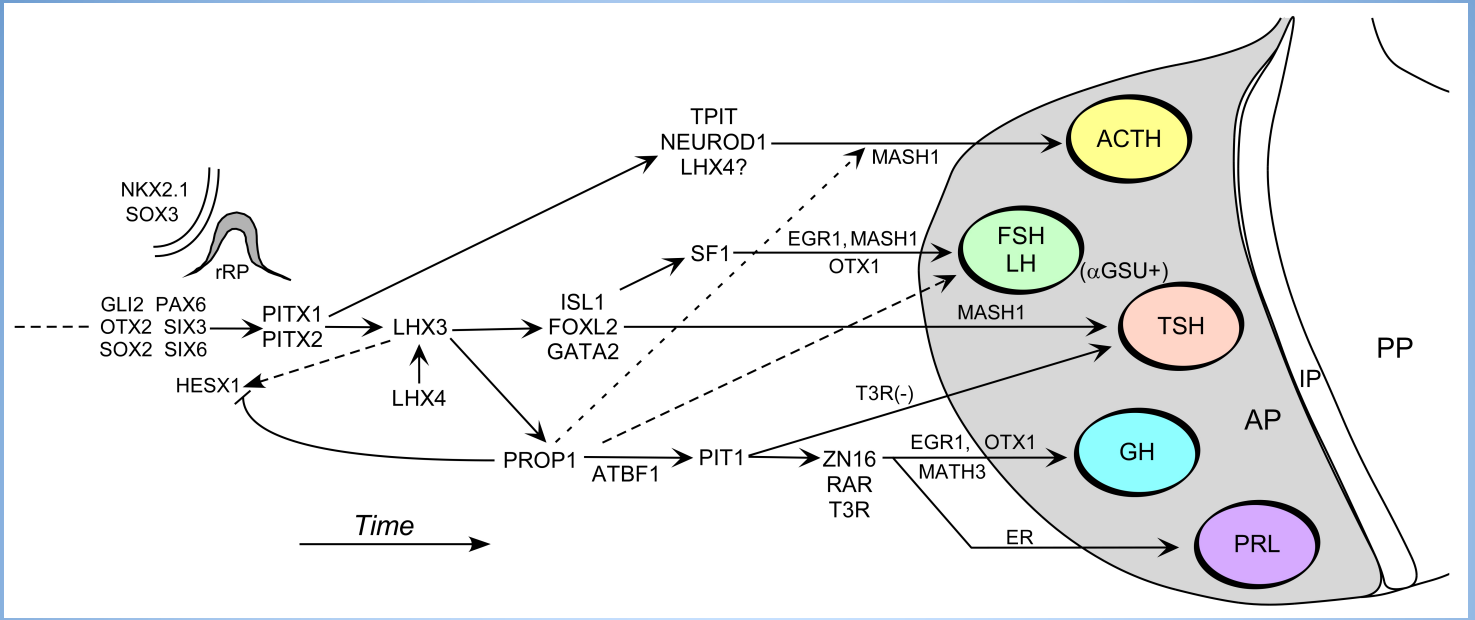
Five cell types of anterior pituitary

15-20%	**Corticotrophs**	POMC -> ACTH
40-50%	**Somatotrophs**	GH
10-20%	**Lactotrophs**	PRL
10-15%	**Gonadotrophs**	LH/FSH
3-5%	**Thyrotrophs**	TSH

% pituitary cell population

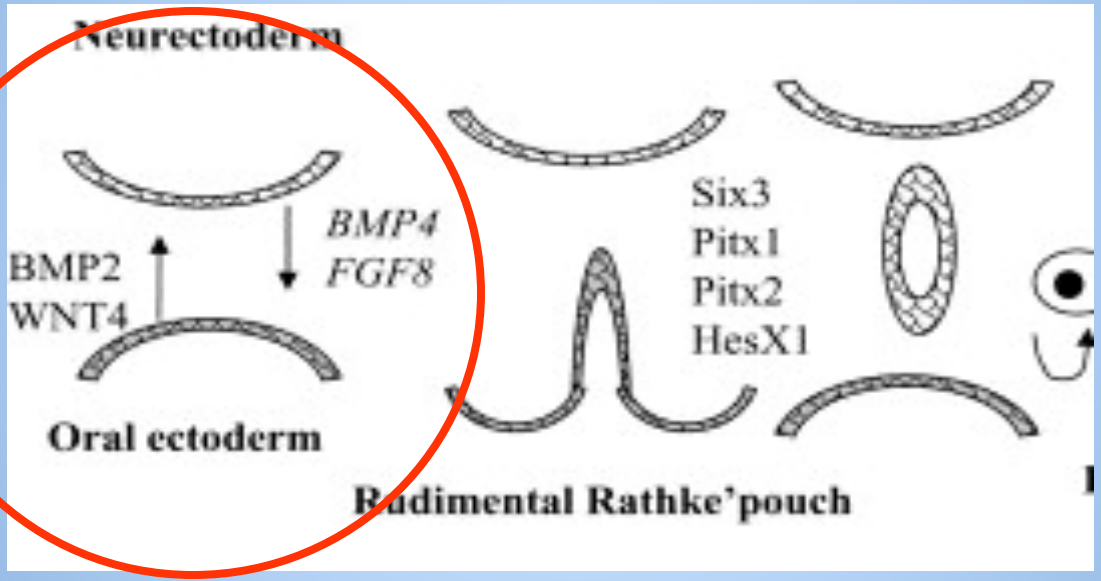
3 stages of anterior pituitary development

1. Induction of pituitary placode – thickened plate of ectoderm
2. Formation of Rathke's pouch - the primordium of the anterior pituitary which undergoes cell proliferation and determination
3. Terminal differentiation of 6 hormone secreting lineages

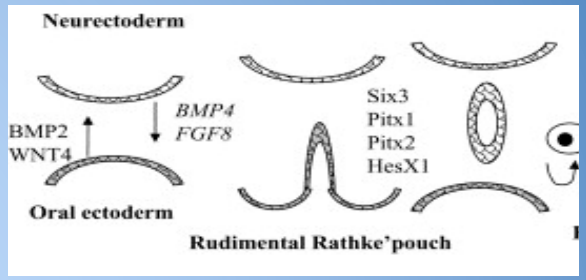


Regulation of the development of the anterior pituitary gland by transcription factors. Following, inductive signals between the developing diencephalon and the oral ectoderm, early transcription factors guide the formation of rudimentary Rathke's Pouch (rRP) and then subsequent gene regulatory pathways control the determination, proliferation, and differentiation events that establish the specialized hormone-secreting cells.

Induction of pituitary placode



Physiology of anterior pituitary development



Evagination of oral ectoderm –induced by ventral diencephalon

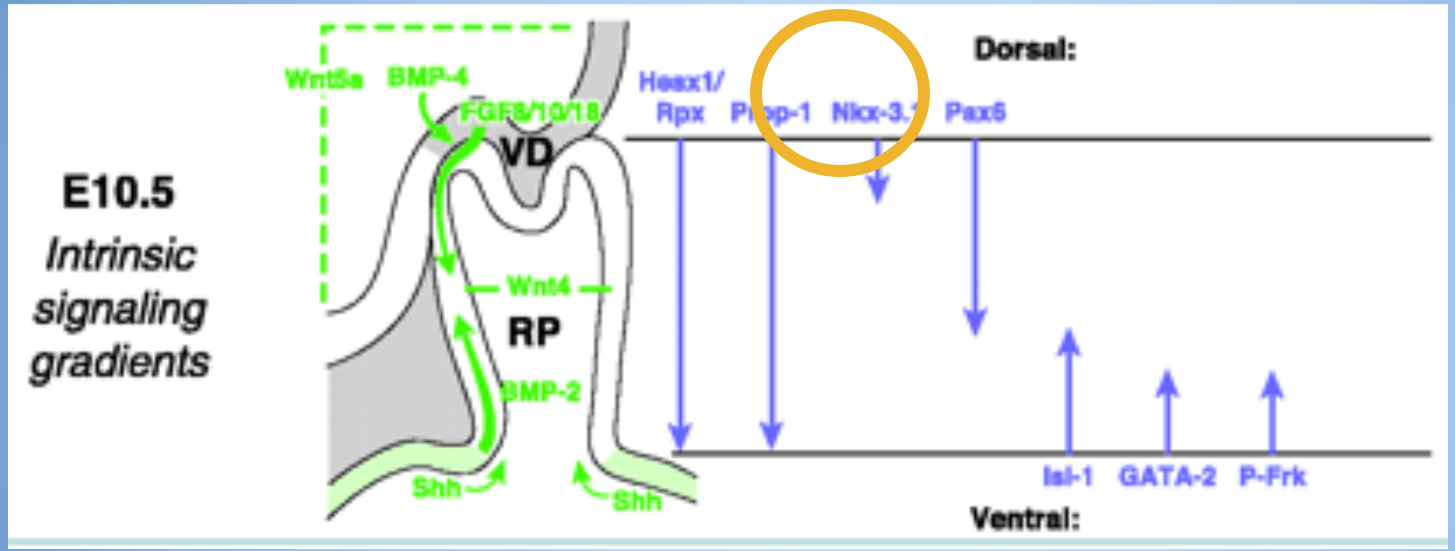
- BMP4 – required for organ commitment of ant pit gland
- FGF8 – opposes BMP2 and is essential for cell survival

Rudimentary Rathke's pouch produces signaling proteins

- BMP2 – provides ventralizing cue
- WNT4 – cellular proliferation

Antagonistic relationship between signals

Early transcription factors



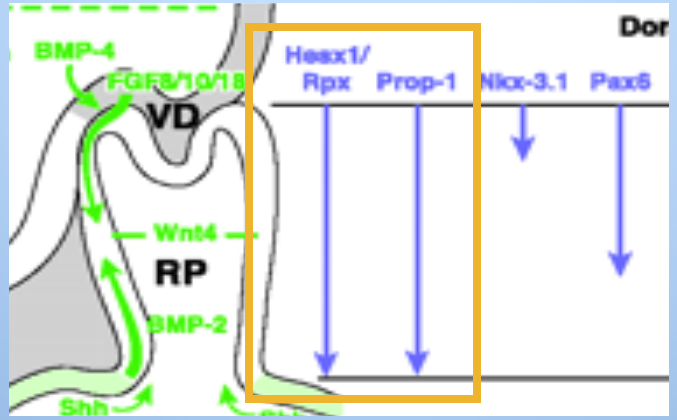
Expansion of Rathke's pouch begins with cellular proliferation induced by
early transcription factors:
PITX1, PITX2, LHX3, LHX4, HESX1, SIX6

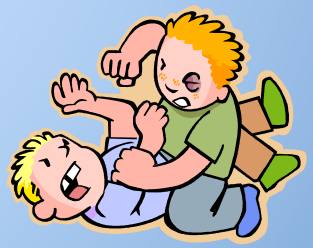
HESX1 – paired-like class of homeodomain transcription factor

REPRESSOR and acts by recruiting co-repressors

Mechanism for temporal organization – eg. HSX1 and PROP1

HSX1 heterodimerizes with PROP1 - inhibits gene activation properties





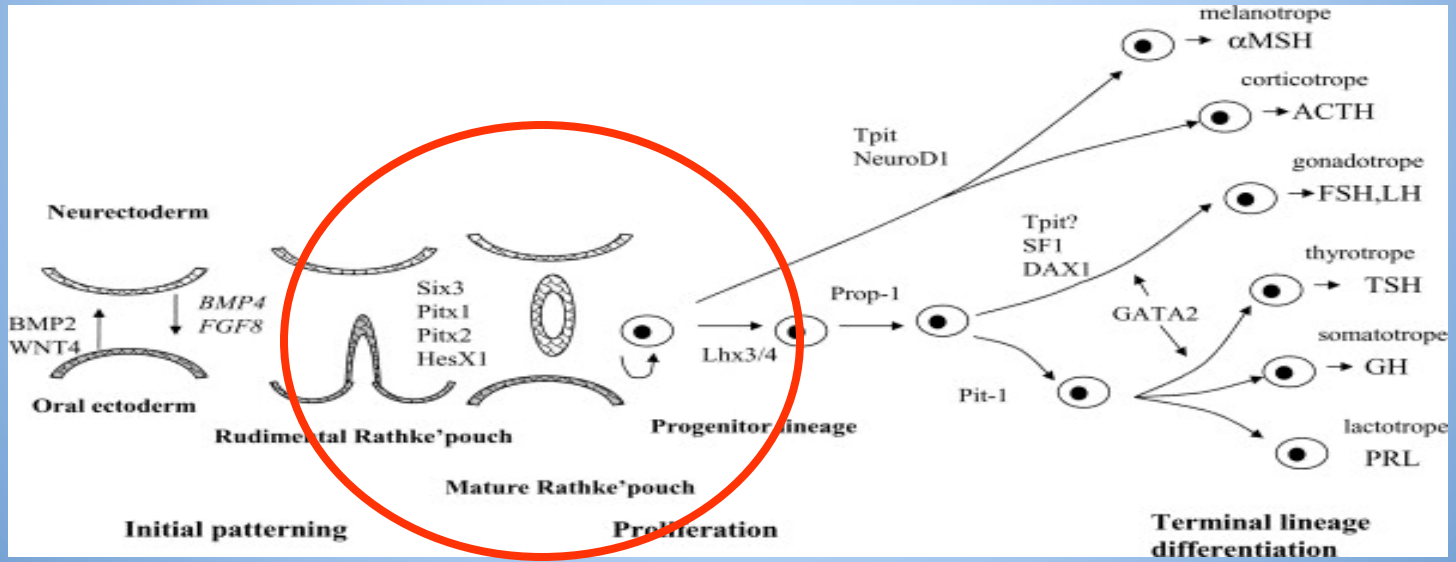
Disorder of HSX1

Recessive or dominant inheritance
Important for development of optic nerve
Clinical manifestation:

- Anterior pituitary hypoplasia/ectopic post pituitary/absent infundibulum
- Absent corpus callosum
- *What d/o does this sound like?*
  - **SOD**

LHX3 - LIM homeodomain transcription factor

LHX3 is essential for proliferation and differentiation of almost all pituitary cells except corticotropes



Disorder of Lhx3

Recessive inheritance

Lhx3 mutations cause

- deficiency in GH, PRL, TSH, LH, FSH
- Rigid cervical spine
- Hypo or hyperplastic anterior pituitary

Disorders of PROP1

Recessive inheritance

PROP1 mutations cause failure of initial proliferation

- PIT1 dependent cell types
- Gonadotropins

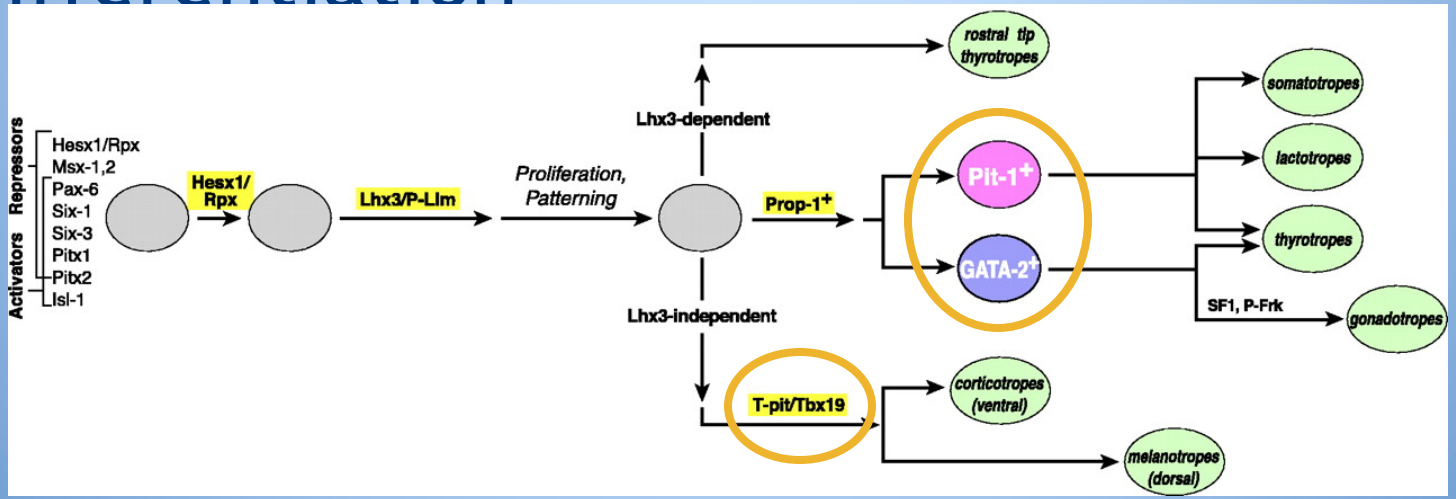
Limited elbow extensibility, blue sclera, large sella turcica

MRI can show hyperplastic anterior pituitary – pseudotumor

(absence of PROP1 results in unopposed persistence of HESX1 expression which is involved in initial exponential proliferation)

Terminal lineage differentiation

More specific transcription factors are responsible for terminal cell type differentiation



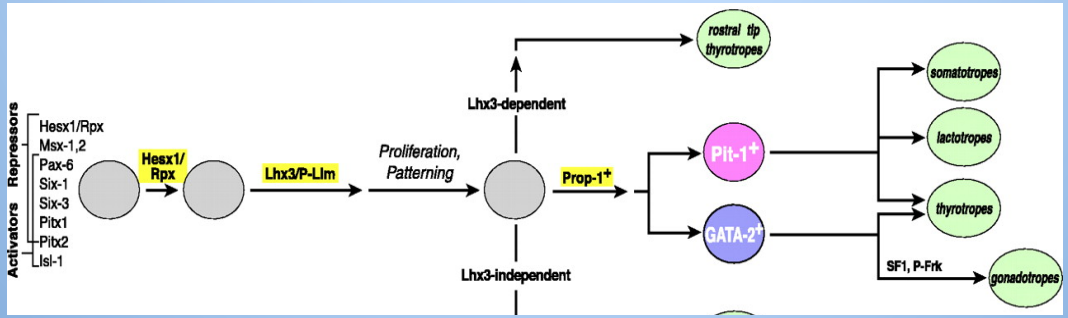
POUF1domain protein

1. Directly controls regulatory genes
   - Required for terminal differentiation of:
     - Somatotrope
     - Lactotrope
     - Thyrotrope
2. Protects from programmed cell death
   - Inactivation of POUF1 from a dominant negative mutation leads to decreased growth rate and cell death
   - Hypoplasia of the gland

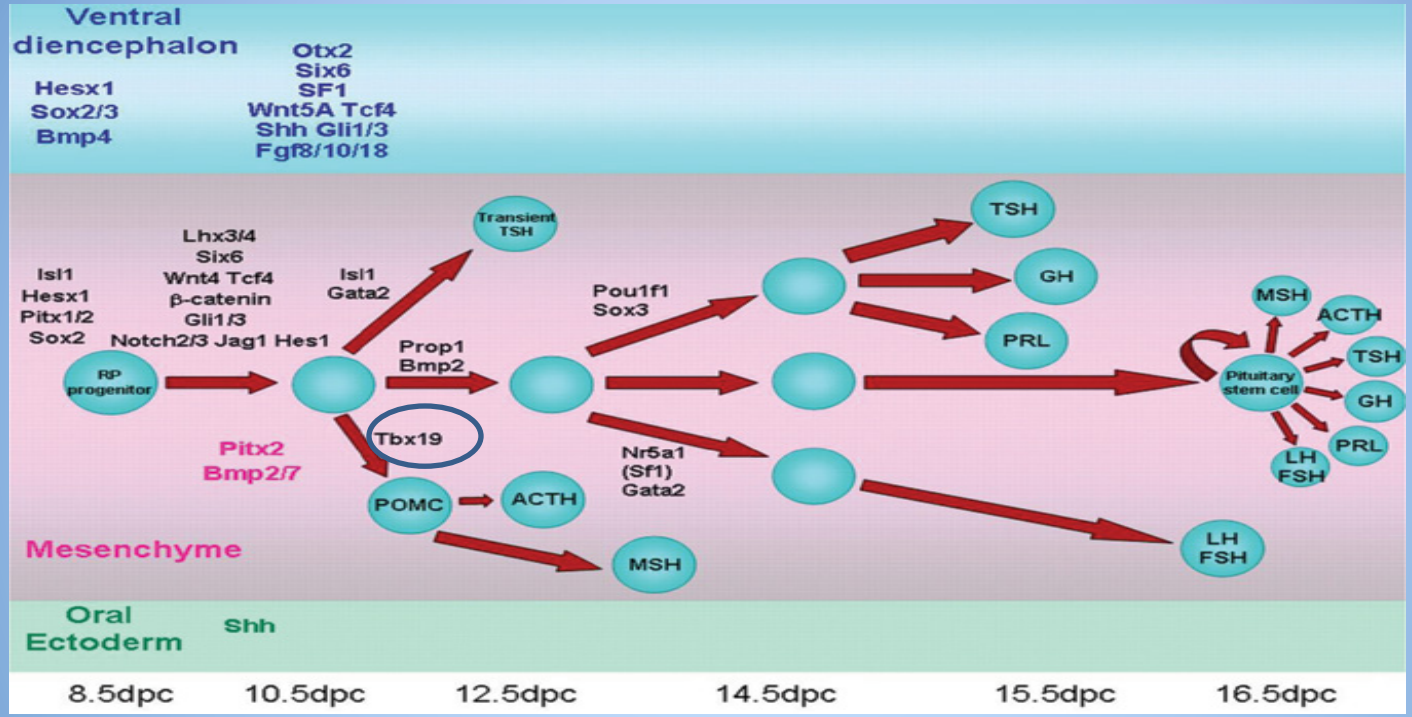
POUF1 domain protein

Model - transition from positional identity to cell-autonomous commitment

Spatial interaction - targeted expression of PIT1 ventrally can convert gonadotropes to thyrotropes - dorsal expression of GATA2 can convert all PIT1-dependent cells to gonadotropes

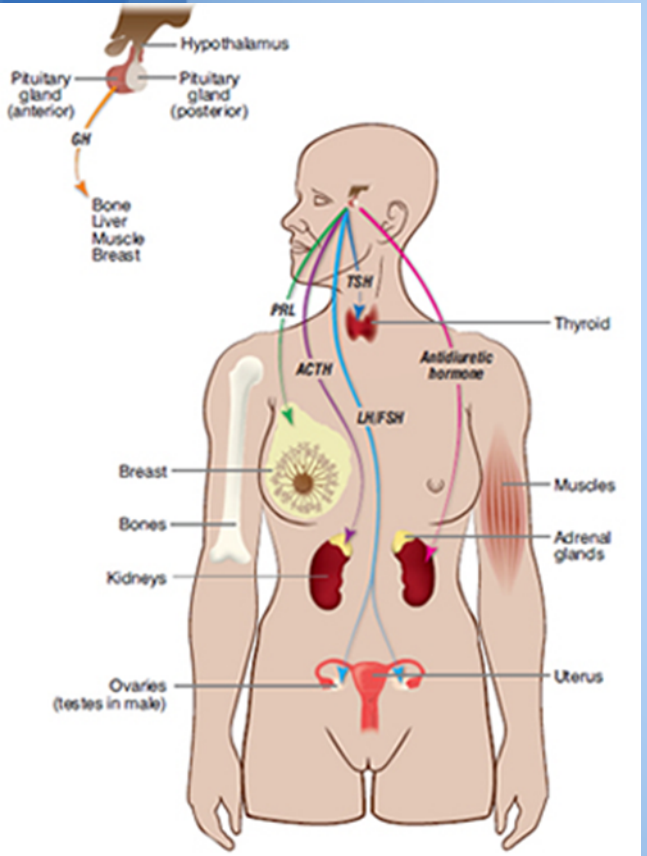


Terminal lineage differentiation

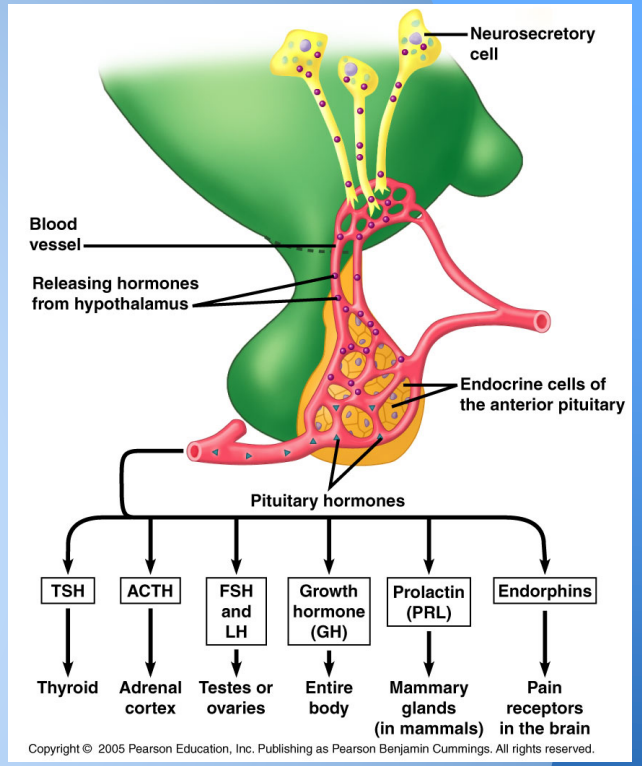


Tbx19 – T box transcription factor
Specific to corticotrope lineage
Activate POMC promoter

Hypopituitarism



Lack of one or more pituitary hormones leading to a loss of function in the gland or organ controlled by that hormone



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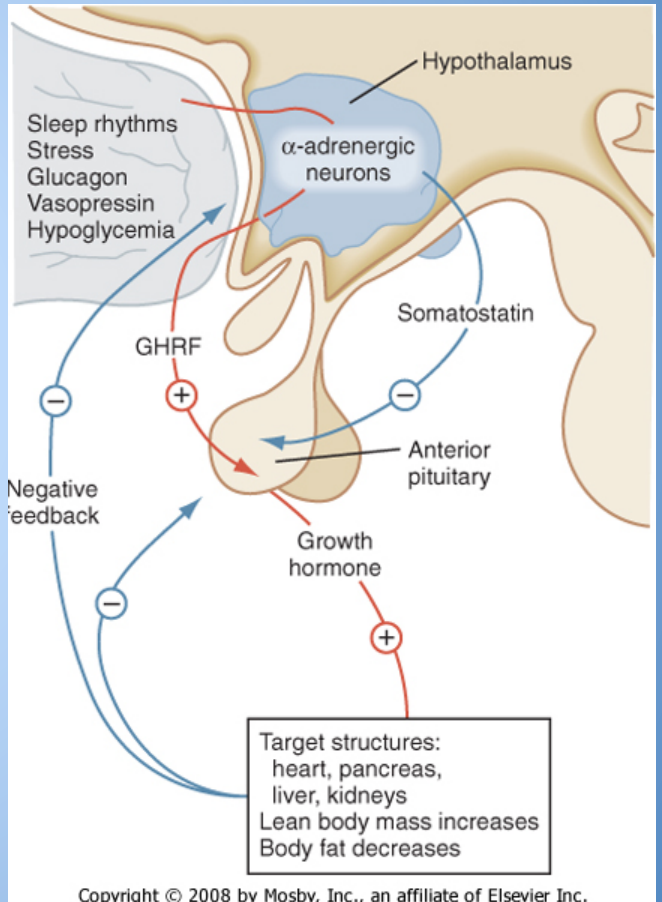
Anterior Pituitary Hormones

- Growth Hormone – stimulates growth of tissues and bone; lipolysis
- ACTH – Stimulates the adrenal gland to release cortisol to maintain blood pressure and blood sugar
- LH/FSH – controls sexual function and fertility
- TSH – Stimulates thyroid gland to release thyroid hormone
- Prolactin – stimulates female breast development and milk production

Growth Hormone

- Secretion
  - GH-releasing factor
- Inhibition
  - Somatostatin
- Stimulates most body cells to increase in size and divide
- Major targets are bone and skeletal muscle
- Promotes protein synthesis
- Encourages use of fats for fuel thus conserving glucose
- Most effects are mediated either directly or indirectly by IGFs



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GH deficiency

- In children -> slowing or lack of growth and an increase in body fat
- Infants with GH deficiency are NOT born SGA. They are normal weight and length at birth.
- In childhood hypopituitarism, GH is the most commonly affected
- Incidence rate of 1:3500 in US

  47% due to tumors (craniopharyngioma)

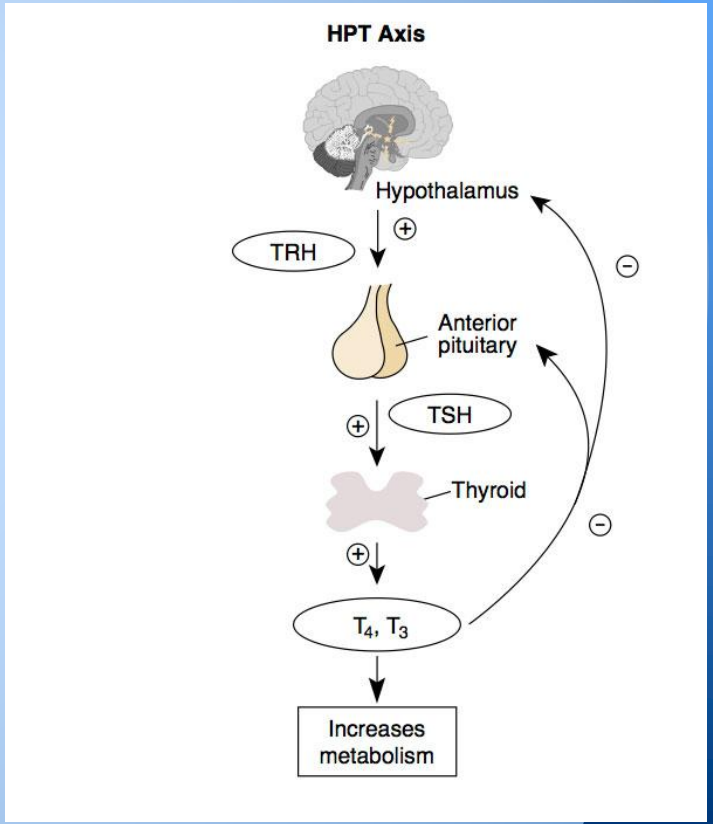
  15% CNS malformation

  14% SOD

  Radiation, leukemia, trauma, histiocytosis and CNS infection

Hypothalamic Pituitary Thyroid Axis

- Hypothalamus senses low T3 & T4 and releases TRH
- Anterior pituitary releases TSH & prolactin
- Thyroid makes T3 & T4



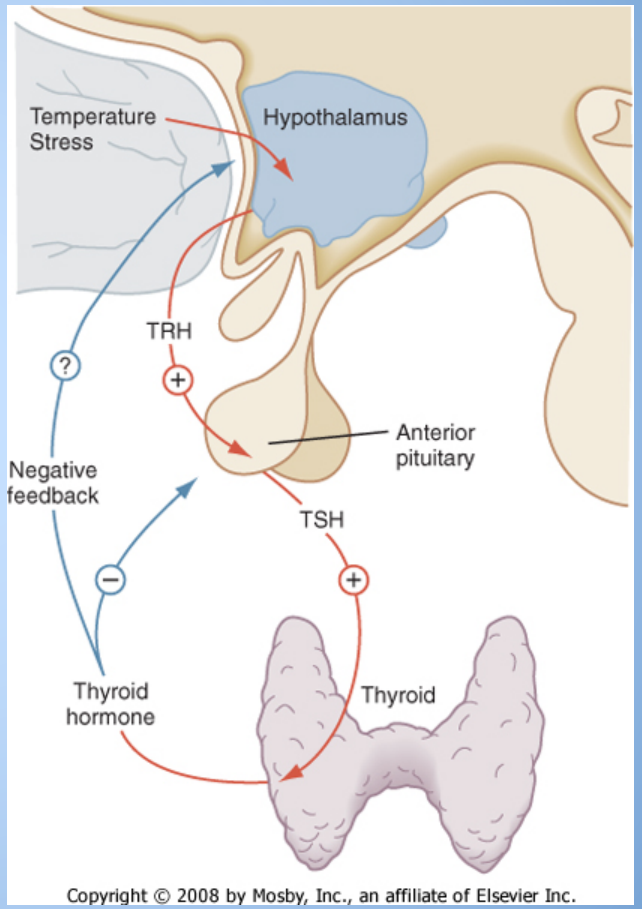
TSH

Secretion
- TRH

Inhibition
- Thyroid Hormone

Actions
- Increases iodide uptake, thyroglobulin and thyroid hormone synthesis

Deficiency is a cause of congenital hypothyroidism



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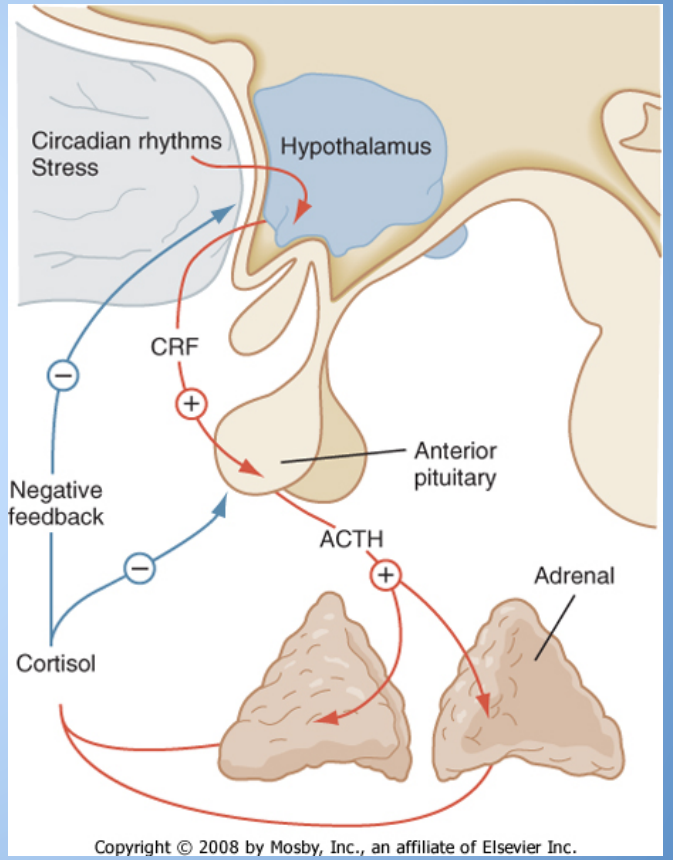
ACTH

Secretion
- CRF from hypothalamus
- Pro-opiomelanocortin (POMC)
  - ACTH
  - endorphins
  - Melanocyte stimulating hormones

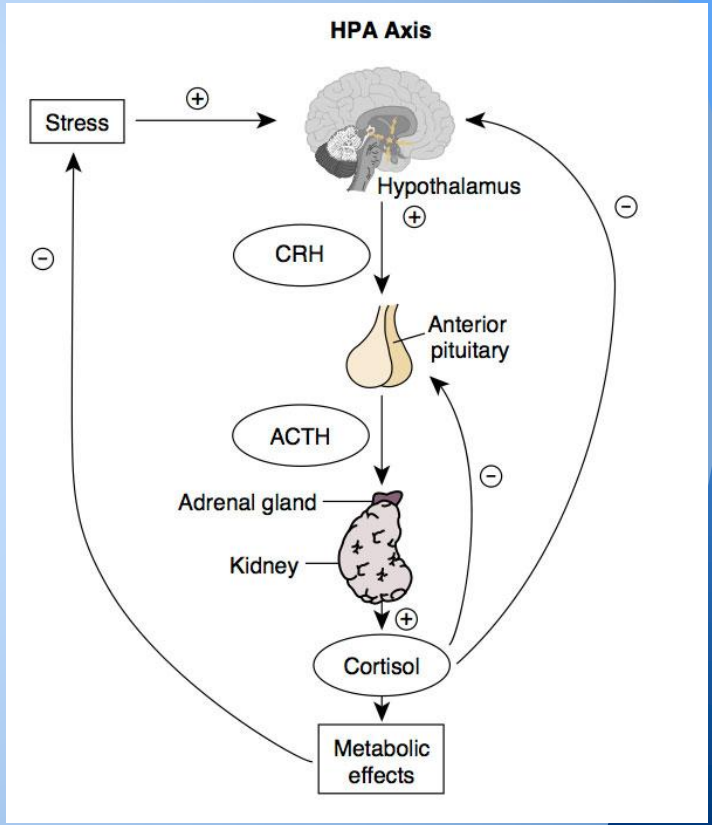
Inhibition
- Cortisol from adrenals
- Prolonged steroid use

Infants do not establish a diurnal pattern of cortisol release until 6 months of age.



Hypothalamic Pituitary Adrenal Axis

- Hypothalamus senses low cortisol or threat to homeostasis
- Releases CRH
- Ant pituitary releases ACTH
- Adrenal gland makes cortisol
- Cortisol → negative feedback loop on pituitary and hypothalamus
- ADH also causes release of ACTH

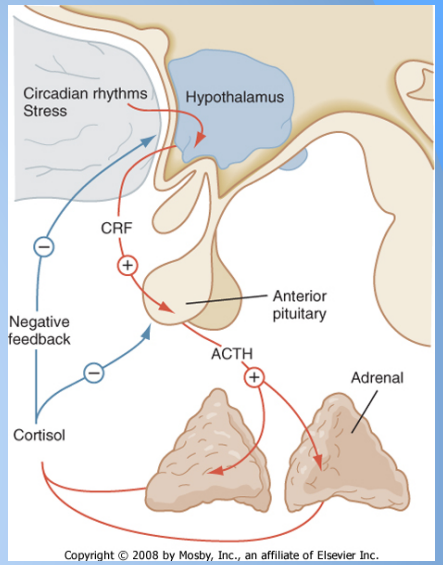


ACTH deficiency

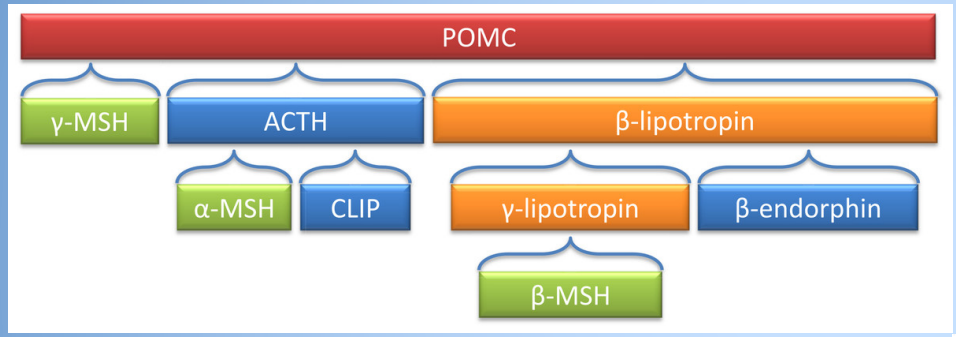
Symptoms include weakness, fatigue, weight loss, abdominal pain, hypotension, hypoglycemia and hyponatremia (with normokalemia) – unlike CAH because mineralocorticoid function regulated by the RAS

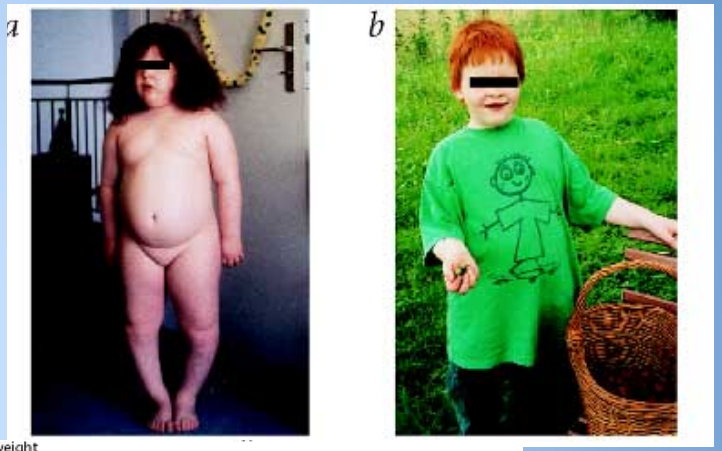
Hyponatremia in adrenal insufficiency is due to inappropriate increase in vasopressin secretion/action (cortisol Nly exerts tonic inhibitory effect on vasopressin secretion) and inability to excrete free water

- Severe stress - infection or surgery – precipitate adrenal crisis, coma and death

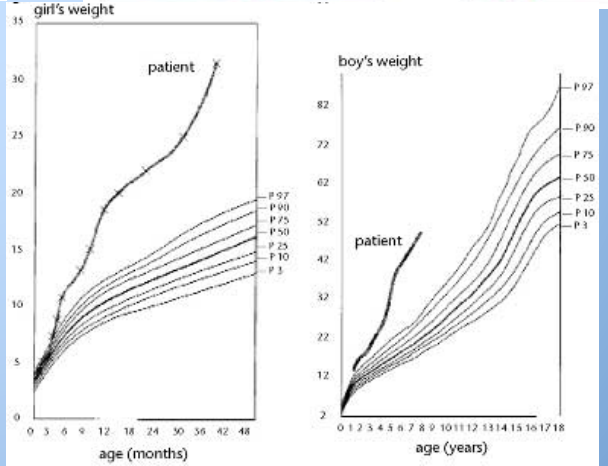


Isolated ACTH Deficiency



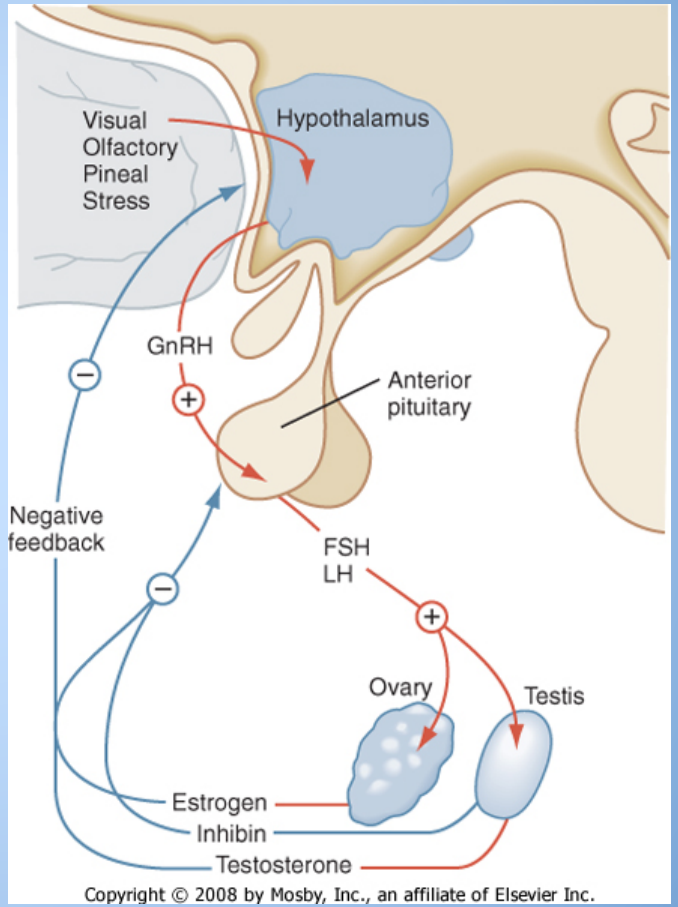


Adrenal insufficiency: hypoglycemia, cholestasis, and hyponatremia
Hypopigmentation with red hair
Early onset morbid obesity



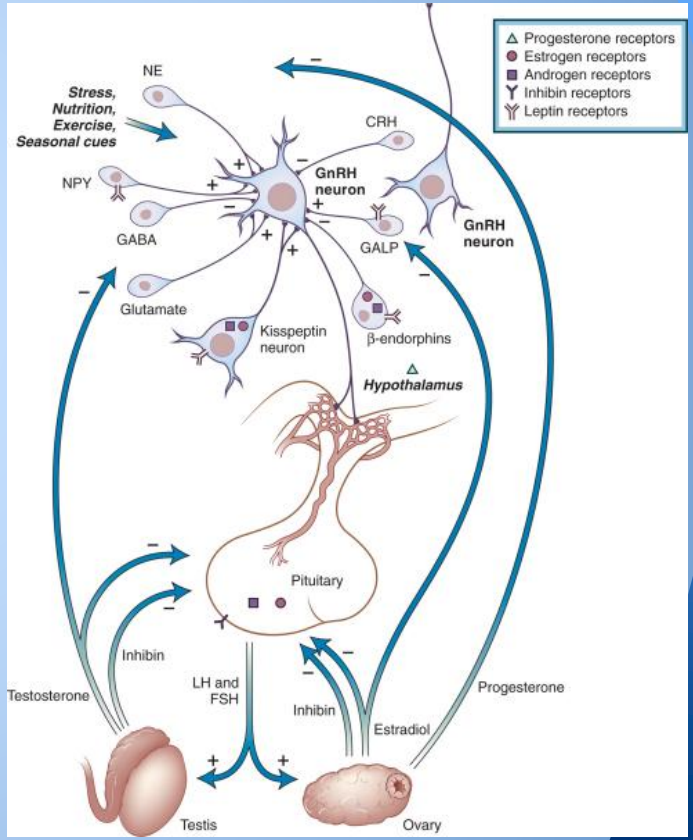
Gonadotropins

- Secretion
  - GnRH
  - Hypothalamus sends pulses
    - Increases during puberty
  - Inhibition
    - Inhibin
  - FSH
    - Spermatogenesis
    - Follicular maturation
  - LH
    - Testosterone
    - Estradiol



Hypothalamic Pituitary Gonadal Axis

- Hypothalamus senses low sex hormones
- Releases GnRH
- Ant pituitary releases LH & FSH → estrogen & testosterone production
- Gonads produce inhibin → neg feedback
- Pituitary produces follistatin, which inhibits activin → neg feedback



Prolactin

- Most important regulator is dopamine which acts on D2 receptors of lactotrophs causing INHIBITION of prolactin secretion
- TRH has a stimulatory effect on prolactin release
- Prolactin suppresses GnRH secretion

Hyperprolactinemia

Galactorrhea

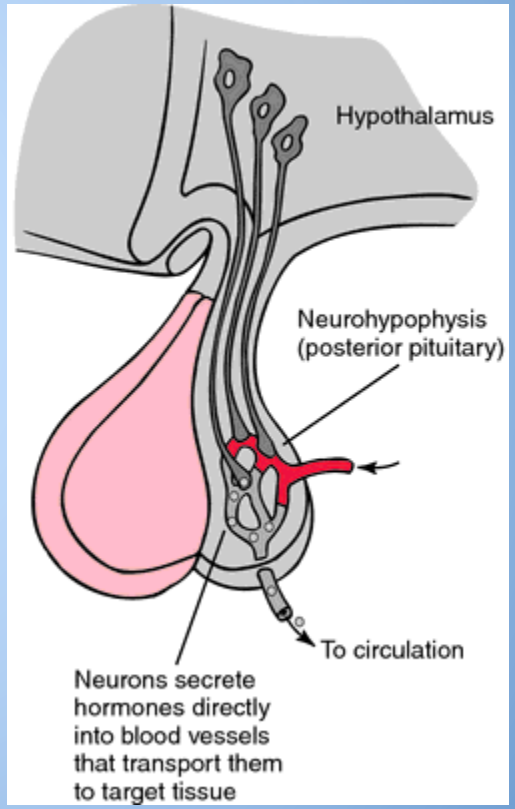
Pituitary adenomas

Medications that can cause hyperprolactinemia

Neuroleptics, antipsychotics, estrogens and anti-hypertensives

Hormones of Posterior Pituitary

- Paraventricular nucleus and supraoptic nucleus produces:
  - Oxytocin - uterine contraction, lactation
  - Vasopressin -water reabsorption from distal and collecting tubule of kidney; concentrate urine.



Posterior Pituitary

- Vasopressin (AVP or ADH)
  - Released in response to increased osmotic pressure in the blood
  - Water balance
    - Increased reabsorption of water in collecting ducts of kidneys
    - Arteriolar vasoconstriction – HTN
    - Increased thirst
  - Overproduction
    - Head trauma, brain tumors, encephalitis, pneumonia
    - SIADH
      - HA, apathy, nausea, vomiting, impaired consciousness
      - Decreased plasma osmolarity
  - Underproduction
    - Central Diabetes Insipidus (DI)
      - Pituitary tumors, head trauma, infiltrative diseases, autoimmune or surgical
      - Increased plasma osmolarity

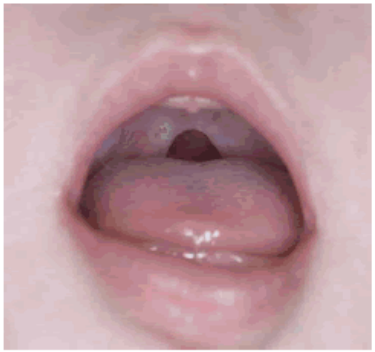
Posterior Pituitary

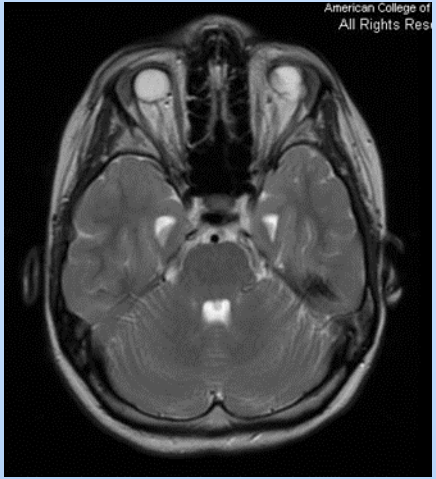
Oxytocin

- Stimulates the smooth muscle of the uterus to contract, inducing labor.
- Stimulates the myoepithelial cells of the breasts to contract which releases milk from breasts when nursing.
- Stimulates maternal behavior.
- In males it stimulates muscle contractions in the prostate gland to release semen during sexual activity

Clinical Presentation of Congenital Hypopituitarism

Figure 2a: Patient with an isolated cleft palate. The external appearance of the face is normal





Congenital Hypopituitarism

- Manifestations that suggest congenital anterior hypopituitarism include midline defects, micropenis, optic atrophy, hypoglycemia, and poor growth.
- Can occur from birth trauma, asphyxia, part of a number of midline defects, or due to a genetic mutation involving the anatomic development of the pituitary gland.

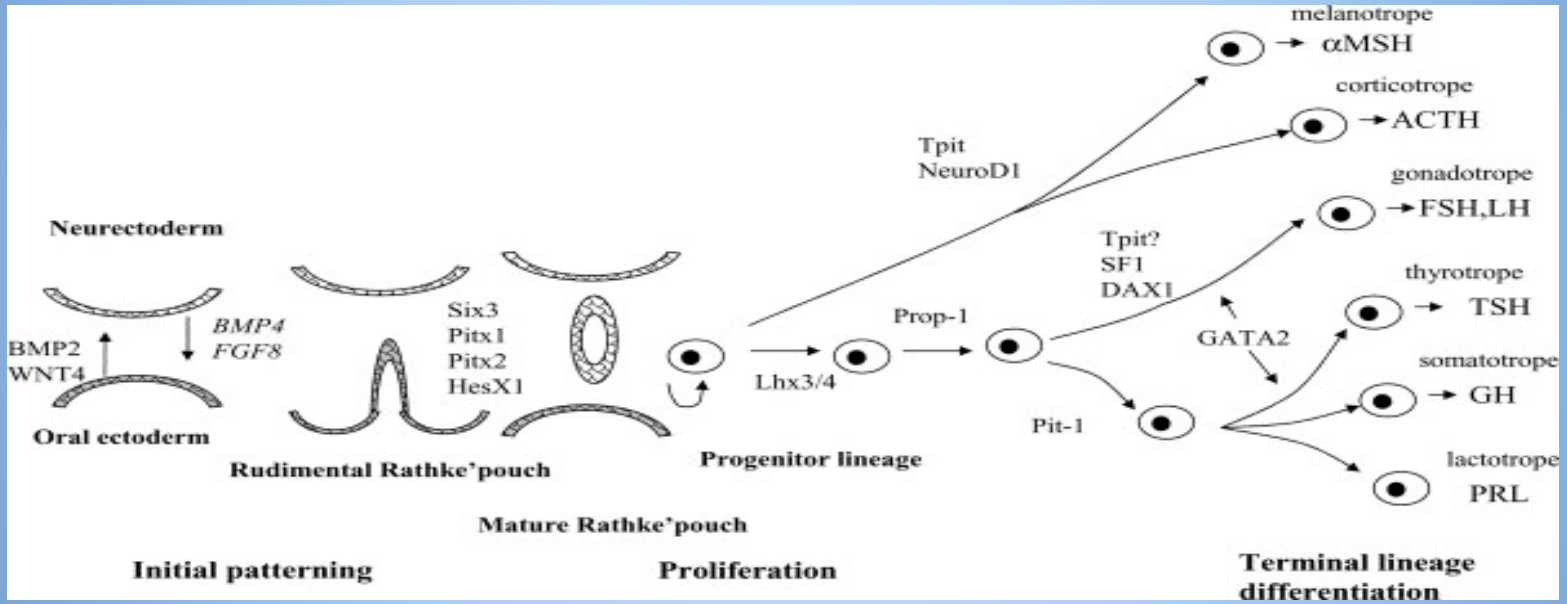
Congenital Hypopituitarism: Midline Defects

- Most common midline defect is septo-optic dysplasia.
- This disorder includes absence of the septum pellucidum in 50% of cases and underdevelopment of the optic nerves, associated with variable degrees of reduced vision ranging from mild loss to complete blindness.
- Affected children may present with nystagmus.
- For any child noted to have optic nerve hypoplasia, at least a one-time referral to a pediatric endocrinologist is warranted, especially if there is any associated growth delay.
- Other midline associations with hypopituitarism include the presence of a fused deciduous upper central maxillary incisor cleft lip and/or palate, choanal atresia, anomalous and/or absent vascular supply to the central nervous system, and encephaloceles

Congenital Hypopituitarism: Genetic Defects

- One of the earliest known transcription factor genes involved in embryogenesis of the pituitary gland is Rathke's pouch homeobox, (called *HESX1)*, mutations of which have been found in a few cases of septo-optic dysplasia.
- Other early transcription factor genes important in the formation of various pituitary cell populations are *LHX3*, *LHX4*, and *PROP-1* (Prophet of Pit-1), and *PIT-1/POUF1*. Mutations of *LHX3* are associated with deficiencies of all anterior pituitary hormones ACTH along with a rigid cervical spine leading to limited head rotation,
- *PROP-1* mutations are associated with deficiencies of GH, prolactin, TSH, and sometimes gonadotropins and ACTH, limited elbow extensibility, blue sclerae, and, a large sella turcica in some
- *PIT-1/POUF1* is a pituitary-specific transcription factor that is necessary for the development of somatotroph, lactotroph, and thyrotroph lineages, so mutations of PIT-1 are associated with deficiencies of GH, prolactin, and TSH.

Congenital Hypopituitarism



Septo-Optic Dysplasia/Optic Nerve Hypoplasia

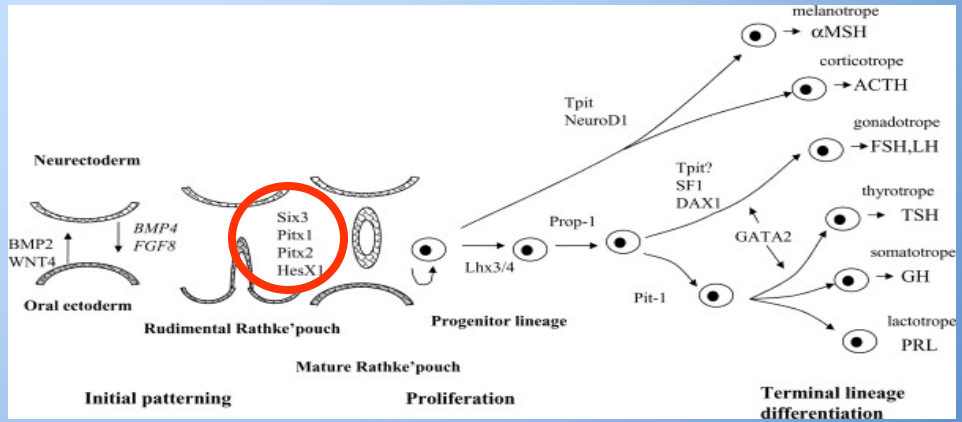
Triad of:

- Hypoplastic optic disk with characteristic double margin
- Absent septum pellucidum and corpus callosum
- Pituitary hormone abnormality – most commonly GHD

Highly variable phenotype

60% have isolated hypopituitarism

30% have all 3 manifestations



Optic disk double margin

- Due to underdevelopment of the optic nerves
- Variable degrees of reduced vision ranging from mild loss to complete blindness.
- Affected children may present with nystagmus
- Any child noted to have optic nerve hypoplasia, a one-time referral to a pediatric endocrinologist is warranted, especially if there is any associated growth delay

SOD

Neonates with nystagmus must have pituitary function evaluated

Symptoms of Congenital Hypopituitarism

- Most common symptom is hypoglycemia due to GH deficiency with or without ACTH deficiency
- Cortisol and GH are counter-regulatory hormones that protect against hypoglycemia
- Without one or both, insulin acts in an unopposed fashion
- In any term infant who develops hypoglycemia with no underlying risk factor (such as prematurity, intrauterine growth retardation, infant of a diabetic mother, etc), the diagnosis of hypopituitarism must be considered.

Symptoms of Congenital Hypopituitarism

Severe cortisol deficiency may result in presentation with hyponatremia (as cortisol is necessary for the action of ADH to facilitate the excretion of free water by the kidneys) and/or outright shock due to its effects on blood pressure maintenance. If DI were present, shock with hypernatremia would manifest.

Considerations for Congenital Hypopituitarism

- Some children with congenital hypopituitarism develop a unique, noninfectious form of hepatitis. The condition is suspected if there is liver enlargement and abnormal liver function tests (predominantly indicating cholestasis) and is confirmed by the presence of characteristic giant-cell transformation of hepatocytes as seen on biopsy.
- The exact cause of this giant-cell hepatitis is unknown, and the condition usually remits on its own over the first few months of life without any permanent damage to the liver.

Diagnosis of hypopituitarism

- Clinical indications for evaluation of congenital hypopituitarism
  - ✓ #1 Hypoglycemia (GHD/ACTH def)
  - ✓ Micro phallus (GHD/Gndtr def)
  - ✓ Jaundice (GHD/thyroid deficiency)
  - ✓ Growth failure
- Hormone testing

  Gonadotropin window of opportunity

  Newborn screen suffice for thyroid ?

  Serum cortisol - @ 8am ?

  GH stimulation – insulin, glucagon, arginine, clonidine
- Imaging: MRI

Treatment

Hormone deficiency is treated by replacing the deficient hormones. The goals of treatment are to improve symptoms and to replace the deficient hormone or hormones at a level that is as close to physiologically correct as possible.

However, one rule of hormone replacement is that no one dose will suit every patient. Thus, the patient will need to be seen regularly after starting treatment to assess the effect. It often takes time and repeated dose changes to find the optimal dose for each patient.

Treatment

Hormone replacement therapy

1. GHD: GH replacement therapy
2. Central hypothyroidism: Levothyroxine usually ½ the dose needed to treat primary hypothyroidism; follow levels of fT4
3. Gonadotropin deficiency: replace sex steroids vs gonadotropins (estrogen and progesterone or testosterone) needed at puberty [not address fertility]
4. Central adrenal insufficiency: replacement of cortisol; lower dose compared to treatment of CAH 10-15 mg/m2/day; stress hormone therapy

**If patients have multiple pituitary hormone deficiencies, cortisol should always be the first hormone replaced as medications like thyroid hormone or GH can increase the body's need for cortisol.

Treatment

Treatment considerations

- Adrenal replacement before thyroid
- Adrenal replacement may unmask DI (treated with oral desmopressin 0.1-0.2 mg tablets)
- Mineralocorticoid function ?

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- Optical problems - generally not treatable
- Vision, physical, and occupational therapies may be required

Board Question

You have a 1 week old boy in your office for evaluation. Parents tell you that the infant is jittery, irritable, and jaundiced. You note that the penis looks a bit small. Of the following, which is the most likely physical abnormality you will find on examination?

A. Bilateral ear tags
B. Cleft palate
C. Club feet
D. Polydactyly

You are evaluating a patient in clinic and notice the abnormality pictured. Which of the following is most likely to be affected?

A. Growth hormone levels
B. Aldosterone levels
C. Catecholamine levels
D. Insulin levels

You are on call in the PICU and following a very sick patient admitted with meningococcal meningitis. He has not had any urine output in the last 8 hours despite fluid administration. You order a BMP and his Na is 125. What is the most likely cause of the hyponatremia in this patient?

A. Diabetes insipidus
B. Psychogenic polydipsia
C. Inappropriate fluid administration
D. SIADH

Questions?