PATHOPHYSIOLOGY OF ENDOCRINE SYSTEM

for DENTAL MEDICINE

Regulation overview

Hypothalamus-pituitary disorders

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ÚSTAV PATOLOGICKEJ FYZIOLÓGIE LF UPJŠ

Introduction

- Endocrine system is a regulatory system that regulates growth, sex differentiation, metabolism and adaptation of human organism
- A set of secretory cells of mesodermal origin

- Endocrine cells produce chemical messengers called hormones – flow of information between the different tissues and organs
- ES Interacts with nervous system

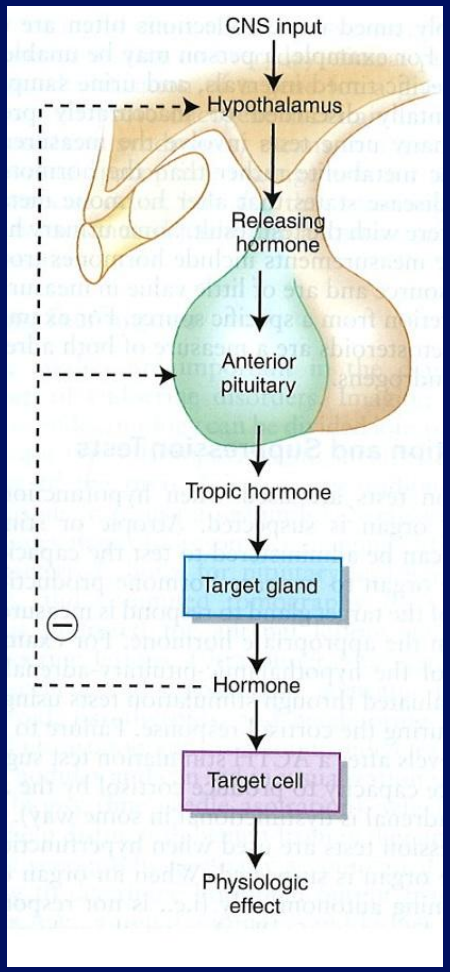
Organisation

- Endocrine cells - organisation
  - Organised into organs – „classical“ glands (pituitary , thyroid, parathyroid, adrenal glands,
  - Discrete areas of endocrine tissue in organs: pancreas, testes, ovaries, hypothalamus
  - Group of cells diffusely localised in organs primarily responsible for different function (ventricle, heart, brain, gut, kidney)

Endocrine regulations

- Plural endocrine glands are regulated in a cascade way through hypothalamic and pituitary hormones
  - Hypothalamic hormones – releasing and inihibiting hormones
  - Pituitary hormones – trophic effect and stimulation of synthesis of peripheral glands hormones

- Tri-level regulatory axes:
  - Axis hypothalamus-pituitary-thyroid gland
  - Axis hypothalamus-pituitary-adrenal gland
  - Axis hypothalamus- pituitary – gonads



Porth, 2014

Endocrine regulation

- Positive feedback mechanism: hormone will stimulate its own production by affecting its relevant releasing or trophic hormone
  - rare
- Negative feedback mechanism: hormone will decrease its own production by affecting its relevant releasing or trophic hormone
  - Prevalent

- The feedback may be provided also by other substances such as metabolic products, minerals, changes in interal environmentE.g.levels of Ca, Na, K, glucose, pH, plasma osmolarity, prostaglandins, fatty acids

Endocrine signalling

- Endocrine – hormone is carried through blood, affects distant cells
- Parakrine – hormone is diffused to extracellular space, affects nearby cells
- Autokrine – hormone affects the same cell
- Intrakrine – signalisation inside of the cell

Chemical structure of hormones

Chemical group:	Derivates of aminoacids	Oligopeptides	Polypeptides	Glykoproteins	Proteins	Steroidal
Hormones	•Epi/norepinephrine • T3, T4 •melatonin	•Vasopressin • oxytoxin •tyreoliberin	•Glucagon •Gonadoliberin • somatostatin • ACTH • endorphins • MSH • kalcitonin	•FSH, LH, TSH	•Insulin • somatotropin •Prolaktin • parathormone	•Gluko-and mineralocorticoids • progesteron • estrogen • testosteron
Produced by:	Adrenal medulla, thyroid gland, epiphysis	hypothalamus	Pancreas, hypothalamus, adenohypophysis, C-cells of thyroid gland	adenohypophysis	Pancreas Adenohypophysis Parathyroid glands	Adrenal cortex, corpus luteum, placenta, ovaries, testes, adrenal glands

Endocrine disorders

Disorders – general classification

According to origin:

- Primary: the cause of disease rises directly from the endocrine gland
- Secondary: the disease is caused by other factor, which affects the gland secondarily, altered feedback mechanism
- Tertiary: may be caused by inadequate tissue sensitivity to hormonal effects

According to location:

- Central: rising from hypothalamus and/or pituitary gland
- Peripheral: rising from peripheral glands (thyroid, adrenal, gonads)

General pathomechanisms

1. Hypo- or hyperfunction of the endocrine gland

- Necrosis, hemorrhage, hypoxia
- Inflammation, autoimmune destruction, tumor, tuberculosis
- Nutrient deficiency (iodine, proteins...)
- Intoxications (licorice-hypermineralocorticolism)
- iatrogenic (corticoids)
- abuse (anabolic hormones)
- Congenital and/or hereditary

General pathomechanism

2. Hormone synthesis disorders

- E.g. congenital adrenal hyperplasia with 21-hydroxylase (or 11b-hydroxylase) deficiency

3. Transport mechanism disorders

- E.g. atranscortinemia – transcortin defect – one of the causes of Addison's disease

4. Receptor disorders

- Reduced/no amount of receptors – androgen insensitivity syndrome
- Increased amount of receptors – hypertension caused by increased amount of angiotensin II receptors (with normal renin activity)
- Receptor structure disorders – vitamin D-resistant rickets
- Antibodies against receptors – autoimmune thyropathies

5. Signal transmission disorders

- E.g. McCune-Albright syndrome – G-protein defect

Hypothalamus
The function

Hypothalamus - functions

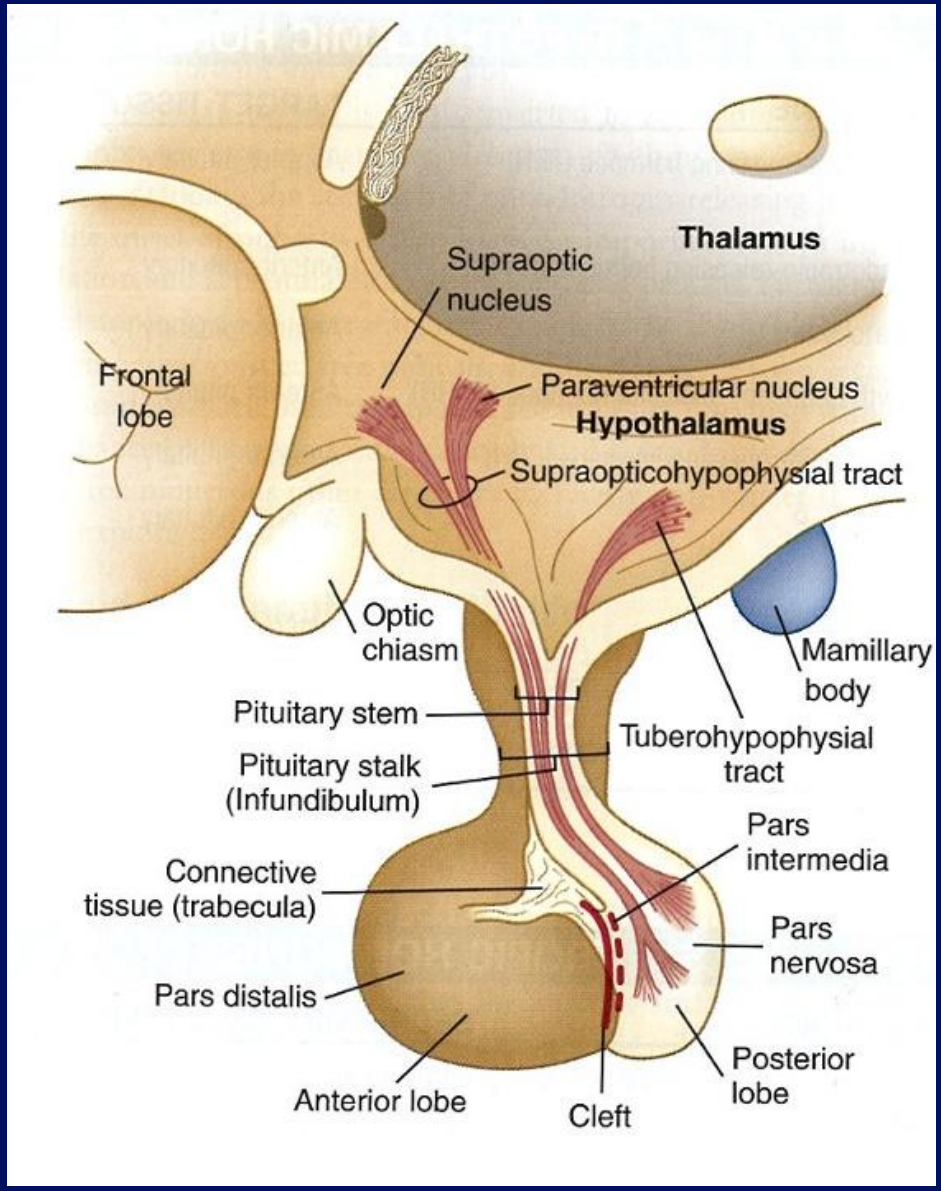
- Hypothalamus-coordination of various stimuli with endocrine system in order to maintain homeostasis
  - Thermoregulation
  - Regulation of ANS, reflex behavior
  - Regulation of amount of fat tissue and energy metabolism
  - Regulation of food intake (orexin A, B, neuropeptide Y)
  - Coordination of stress reaction (integration of immune, inflammatory and endocrine processes)
  - Production of releasing hormones (so called liberins), dopamine, somatostatin
  - Production of vasopressine (ADH) and oxytocin
  - non-endocrine reproductive sexual functions

Hypothalamus

- Hypothalamic nuclei – anatomically on the inferior and lateral wall of 3rd brain ventricle
- Connected to various parts of CNS
- Connected to pituitary gland by axonal and portal vascular system – anatomical and functional connection

Hypothalamus

- Hypothalamus regulates the function of target tissues through pituitary gland creating -
- Neuroendocrine regulatory axis :
  - Hypothalamus – pituitary – endocrine glands – peripheral tissues



McCance, 2019

Disorders of hypothalamus

Ethiology

- Various pathologic processes:
  - Tumors – craniopharyngeom, germinom, gliom, hamartoma
  - Metastases
  - Cyst
  - Hemorrhage
  - Ischemia
  - Sarcoidosis
  - TBC and other infiltrative processes
  - After irradiation (therapeutical)
  - Trauma
  - postsurgical

Symptomatology

2 types of symptoms

- Derived from affected peripheral glands and their produced hormones
- Also affected hypothalamic functions: eating disorders, body mass changes, thermoregulation affected, disorders of sexual behavior, disorders of sleeping, fever, apathy, anorexia

Disorders of hypothalamus - overview

- Hypofunction endocrine hypothalamic syndromes
  - Hypothalamic hypopituitarism
  - Central diabetes insipidus
- Hyperfunction hypothalamic syndromes
  - Pubertas praecox
  - Increased secretion of hypothalamic liberins – tertiary hyperfunction syndromes
- Non-endocrine hyperfunction hypothalamic syndromes
  - Hypothalamic obesity, hyperthermia, increased sexual activity

Hypothalamic hypopituitarism

- Insufficient secretion of one or more hypothalamic liberins
- Ethiology:
  - congenital
  - acquired –
    - organic damage
    - malnutrition
    - strong psychogenic stimuli (long.term and/or repeated stress) supresses function of hypothalamus
    - Strong emotional burden

Hypothalamic hypopituitarism

- Most commonly – isolated deficiency of GnRH or somatoliberin
- Clinical manifestation –
  - Hypogonadism: decreased functions connected to sexual maturation and reproduction
    - Oligomenorea, amenorea, decreased libido, impotence, sterility)
  - Nanism: insufficient growth

Central diabetes insipidus

- Ethiology: autoimmune damage, trauma, tumor, mts, etc

- Pathogenesis: damage of 2 hypothalamic nuclei, which synthesise vasopressin (ADH) – *ncl. supraopticus, ncl. paraventricularis* or a damage to posterior lobe of pituitary– failure of ADH secretion
- Failure to resorb water in collecing ducts of kidneys – massive diuresis (up to 20l/day)
  - Hypoosmolarity of urine – below 200mosm/kg, osmolality lower than blood plasma
  - Hyperosmolarity of blood plasma

  - Different from peripheral diabetes insipidus (renal) – failure of ADH action on tissues (aquaporin or ADH receptor mutations)

Central diabetes insipidus

- Clinical signs:
- Dehydration, hyperosmolarity of blood plasma, hypernatriemia, polyuria of hypoosmolar urine, polydipsia

- - different from diabetes mellitus!

Diabetes insipidus

Also another forms:

- Dipsogenic DI: disorder in the thirst center, where the osmotic threshold to release antidiuretic hormone is abnormally low
- According to some authors – different from primary polydipsia, not due to psychiatric disorder
  - low urine osmolality, normal plasma osmolality, and normal urinary concentrating capacity
  - Polyuria, polydipsia

- Gestational DI: rare complication of pregnancy, usually developing in the third trimester and remitting spontaneously 4–6 weeks *post-partum*.
- Pathomechanism: excessive vasopressinase activity, an enzyme expressed by placental trophoblasts which metabolises arginine vasopressin (AVP).

Pubertas praecox- precocious puberty

- Premature onset of puberty before age 7-8 (girls) and before age 9 (boys)
  - Criteria may differ by race, e.g. earlier in African/Afroamericans

- Ethiology: tumor, inflammation in hypothalamic region, idiopathic
- Pathogenesis: premature secretion of GnRH and premature onset of puberty
- Clinical signs: Premature onset of pubertal features –
  - Thelarche – breast budding, breast development
  - Pubarche – onset of pubic hair growth
  - Menarche – onset of menstration

  - Also tendency to obesity, premature closure of epiphysis of long bones – lifelong short stature

Precocious puberty

- Classification:
  - Partial: onset and progression of one or several pubertal features
  - Complete: : onset and progression of all pubertal features (telarche, menarche, pubarche)
  - Mixed: virilisation of a girl or feminisation of a boy – secondary sex characteristics of the opposite sex

- *Pseudopubertas praecox*: increased secretion of sex hormones by peripheral sexual glands leading to premature puberty

Rare hypothalamic disease - overview

- Frohlich syndrome – hypothalamic obesity and hypogonadism
- Laurence-Moon-Biedl syndrome- hypothalamic obesity, hypogonadism, central diabetes insipidus, retinitis
- Prader-Willi syndrome: hypothalamic obesity, mental retardation, hypogonadism, kryptorchism, low stature
- Syndrome of hypothalamic hypodipsia-hypernatriemia: disorder of fluid intake

Adenohypophysis
Disorders of pituitary gland

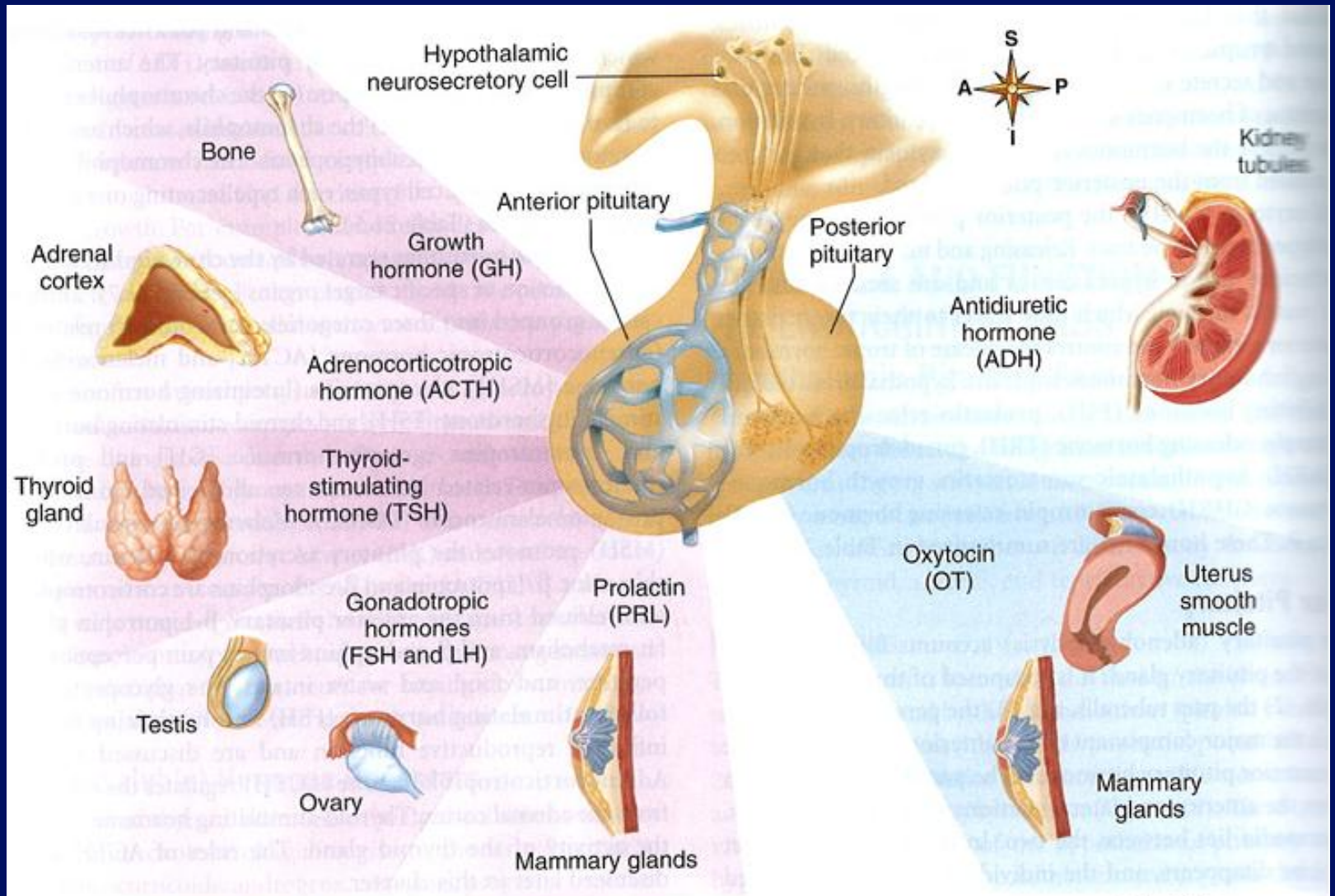


FIGURE 21.7 Pituitary Hormones and Their Target Organs. *FSH,* Follicle-stimulating hormone; *LH,* luteinizing hormone. (From Patton KT, Thibodeau GA: *The human body in health & disease,* ed 7, St Louis, 2018, Elsevier.)

McCance, 2019

Adenohypophysis

- 5 types of secretory cells
  - Tyreotropic cells : TSH
  - Gonadotropic cells (FSH, LH)
  - Kortikotropic cells (ACTH, MSH, beta-endorphins)
  - Somatotropic (GH, STH)
  - Prolactin secerning cells

Disorders of adenohypophysis- overview

- 1. Hyperfunction – hyperpituitarism
  - a) Prolactine producing adenoma (prolactinom)
  - b) Growth hormone producing adenoma
  - c) ACTH producing adenoma (Cushing disease, central hypercorticalism)
  - d) TSH producing adenoma
  - e) Gonadotropin producing adenoma

- 2. Hypofunction - hypopituitarism

1. Hyperpituitarism

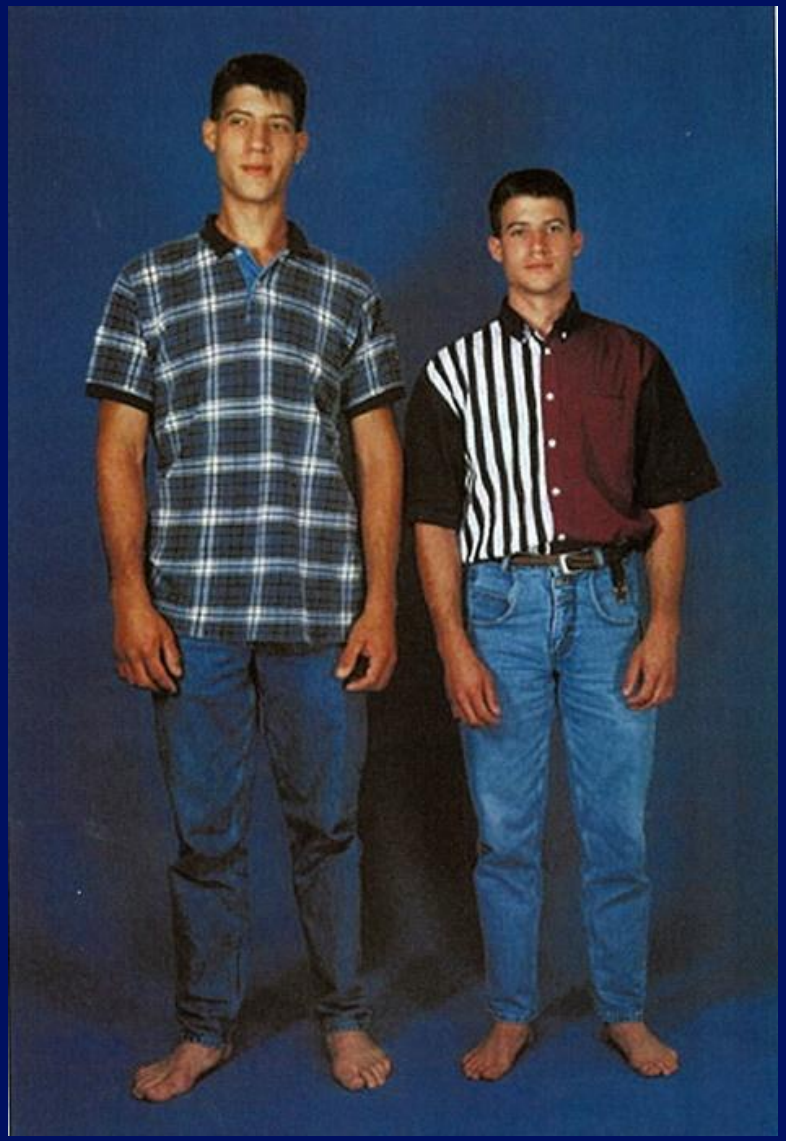
- Etiology:
  - Endocrine active adenomas (most common),
  - malignant tumors,
  - infiltrative inflammatory processes (sarcoidosis, tuberculosis,
  - increased production of liberins in hypothalamus

a) prolactinoma

- Pathomechanism: prolactin decreses secretion of gonadoliberin in hypothalamus and decreses secretion of FSH and LH in adenohypophysis
  - On periphery it inhibits effects of estrogens
  - Result is – hypogonadism –
    - manifestation:
    - Females: disorders of menstruation, decreased sexual functions, impotence, inferility, osteoporosis, galactorea
    - Males: decreased sexual functions, impotence, inferility, osteoporosis , galactorea
      - Galactorea – secretion of milk apart from breastfeeding period or in males

b) Growth hormone producing adenoma

- Continual secretion instead of pulse
- 2 phenotypes – according to timing
  - 1. gigantism: adenoma producing GH before the closure of growth zones in the bones (before termination of pubertal and pospubertal growth)
  - GH stimulates the growth of the long bones
  - 2. acromegaly: adenoma producing GH after the closure of growth zones in the bones
  - Gradual, slow onset of clinical signs (years)



- Porth, 2014

Acromegaly

Clinical signs:

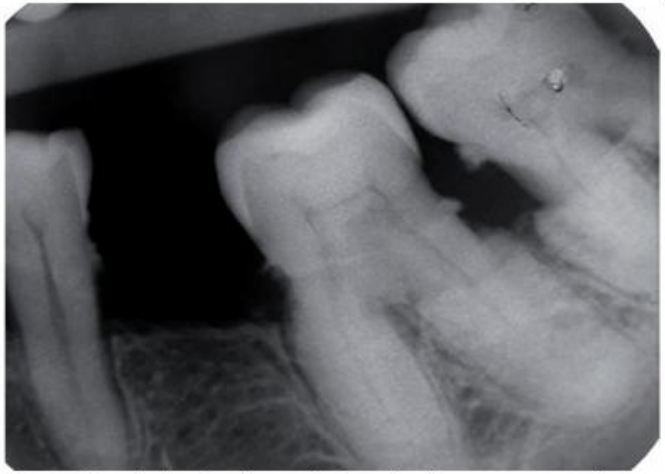
- Enlarged acral parts of body (lips, nose, ears, supraorbital arcs, chin, fingers, thumbs)
- Enlarged spaces inbetween teeth
- Overbite of upper jaw, prognatia, bite disorders
- Macroglossia
- Deepening of voice
- Artralgia (pain in joints)
- Increased body weight
- Radicular pain, paresthesia
- Decreased libido, impotence, oligomenorea, infertility
- Muscles: increased strength, later weakness
- Fatigue
- Hypertrichosis
- Decreased glucose tolerance
- CVS: hypertension, kardiomegaly, heart failure
- Increased sweating
- Decreased heat toelrance
- Skin changes

Acromegaly

Modofied acc.to: Acromegaly - Ujala Cygnus

Large size of tongue in a patient with acromegaly.
Image from 'FIPA Patients' Family Isolated Pituitary Adenoma Patients charity group www.fipapatients.org/disorders/sporadicpituitaryadenomas

Increased space between teeth in a patient with acromegaly.
Image from 'FIPA Patients' Family Isolated Pituitary Adenoma Patients charity group www.fipapatients.org/disorders/sporadicpituitaryadenomas



Intraoral periapical radiograph showing hypercementosis in relation to molars. Roopashri et al, Dental patient with acromegaly: a case report. Journal of oral science, Vol 53, No 1, 2011.

Lateral cephalogram showing enlarged sella turcica, enlarged frontal sinus, steep mandibular angle and class III profile with prognathic mandible.

Roopashri et al, Dental patient with acromegaly: a case report. Journal of oral science, Vol 53, No 1, 2011.

Chan, 2017

Acromegaly

What should dental professionals look for?

Acromegaly may not manifest with clear clinical symptoms, particularly early in progression.[11] This may mean the earliest signs of acromegaly is identified by dental professionals.

Oral manifestations

Observations may include the following:

- Mandibular changes – Thickening of the mandible. Growth in condyle and ramus leading to development of a class III malocclusion in adulthood with an associated mandibular prognathism
- Widening of the maxilla
- Increased height and thickness of alveolar processes
- Occlusal changes - Over-eruption of posterior teeth (compensating growth of mandible). Buccal flaring of mandibular posterior teeth. Increased spacing between teeth, anterior flaring, anterior open bite.
- Hypercementosis
- Macroglossia and associated speech difficulty
- Increased difficulty with chewing
- Ill-fitting dentures
- Jaw and muscular pain
- Radiographic changes. Enlarged sella turcica, enlargement of the paranasal sinuses (especially the frontal sinus), steep mandibular angle and class III profile, Increased gonial angle

Chan, 2017

Acromegaly

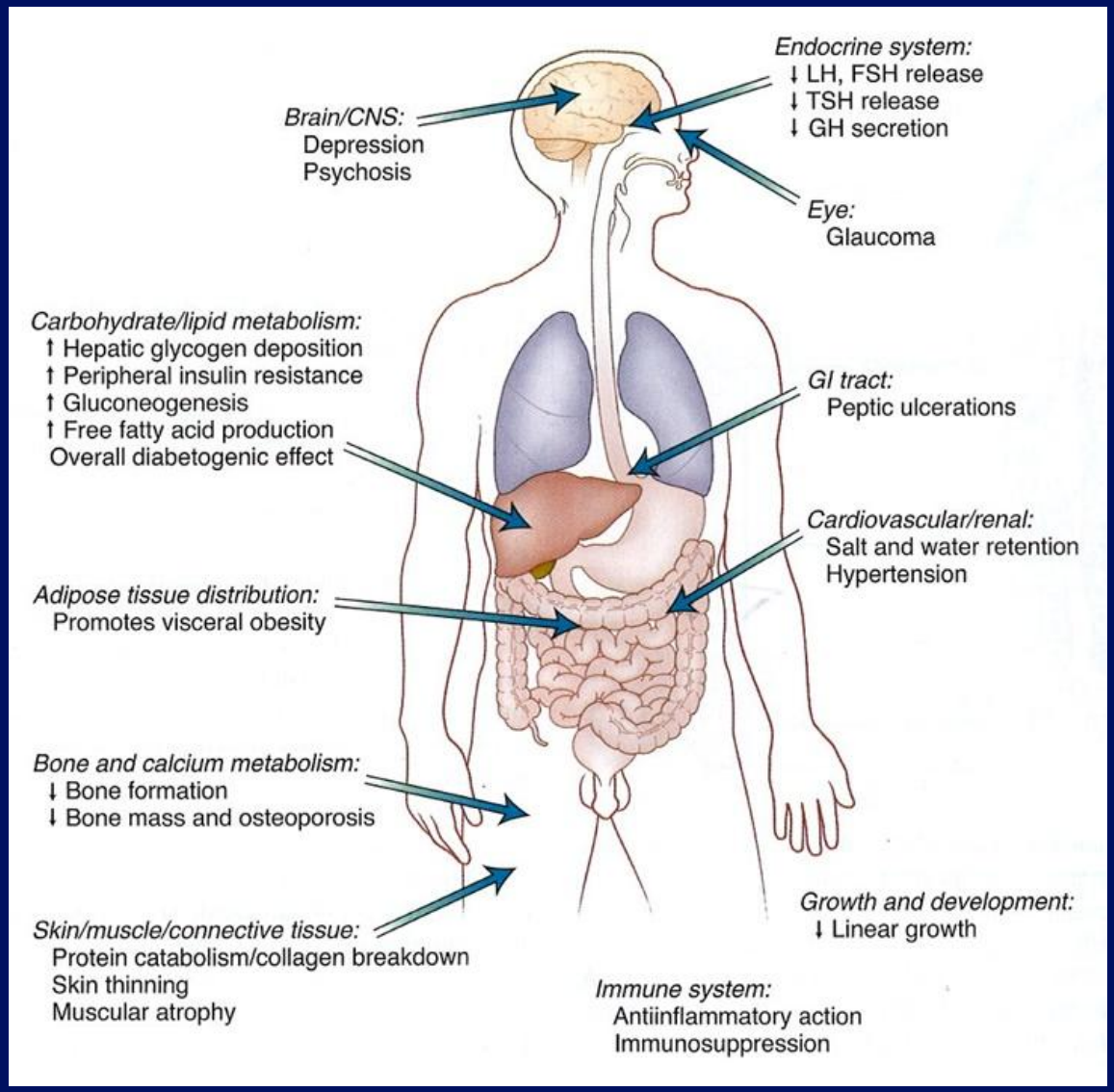
Clinical signs:

- Derived from direct effect of GH to tissues, also due to decreased synthesis of other adenohypophyseal hormones – FSH, LH, TSH
- Not simply an esthetic problem, but is a source of several medical complications
- Cardiovascular complications – the main reason for mortality of patients

c) Adenoma producing ACTH
But firstly...

- Physiological effects of glucocorticoids: (cortisol)
  - A stress hormone
  - metabolic: catabolic, antianabolic, (diabetogenic)
  - Conversion of proteins into glucose, storage of glucose into glycogen, increased resistance of cells toward insulin, lipolysis or lipid accumulation (depending on body place)
  - Stimulation of osteoclasts, decreased intestinal resorption of Ca
  - Immunomodulatory effects: decreases sepcific immune mechanism, delays inflammation
  - Connective tissues: inhibits collagen synthesis and fibroblast proliferation, thickening of skin, capillary fragility, delayed wound healing

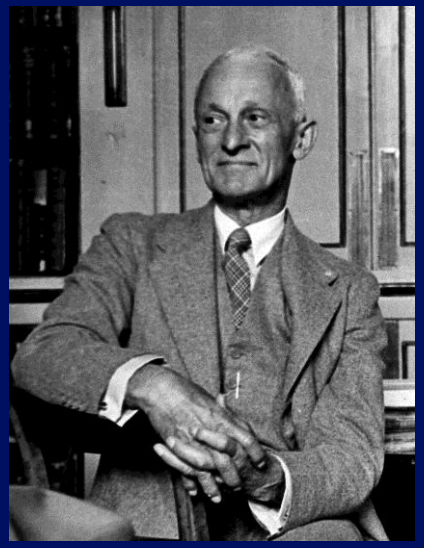
- Physiological effects of mineralocorticoids: (aldosteron)
  - A stress hormone
  - Retention of sodium and retention of extracellular fluid



McCance, 2019

c) Adenoma producing ACTH

- A.K.A. The Cushing´s disease – a central (secondary) hypercortisolism
- Pathogenesis: ACTH stimulates adrenal cortex – hyperplasia of cortex, increased production of glucocorticoids, androgens, to a lesser extend mineralocorticoids
- Clinical signs: observed in several organ systems, developing due to
  - Increased volume of adenohypophysis
  - increased levels of cortisol
  - Decreased levels of other tropic hormones



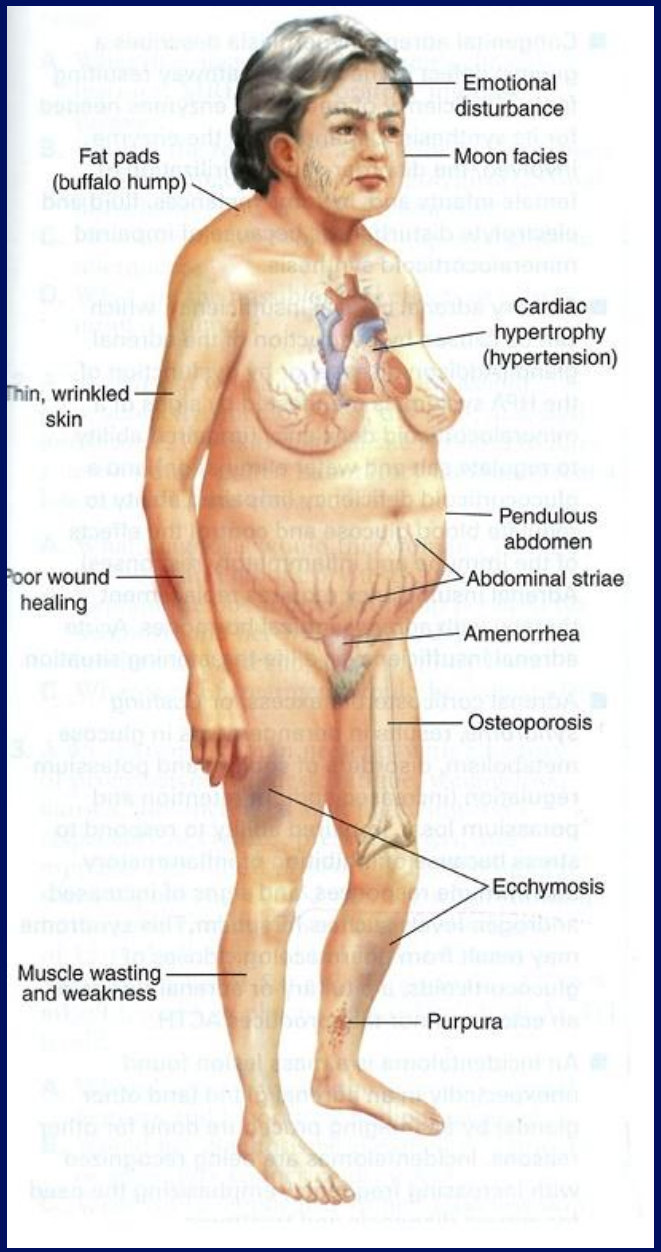
Harvey Williams Cushing (April 8, 1869 – October 7, 1939)

was an American neurosurgeon, pathologist, writer and a drafstman

Cushing´s disease

- Hypercortisolism – increased levels of cortisol in plasma
- Affects several organ systems

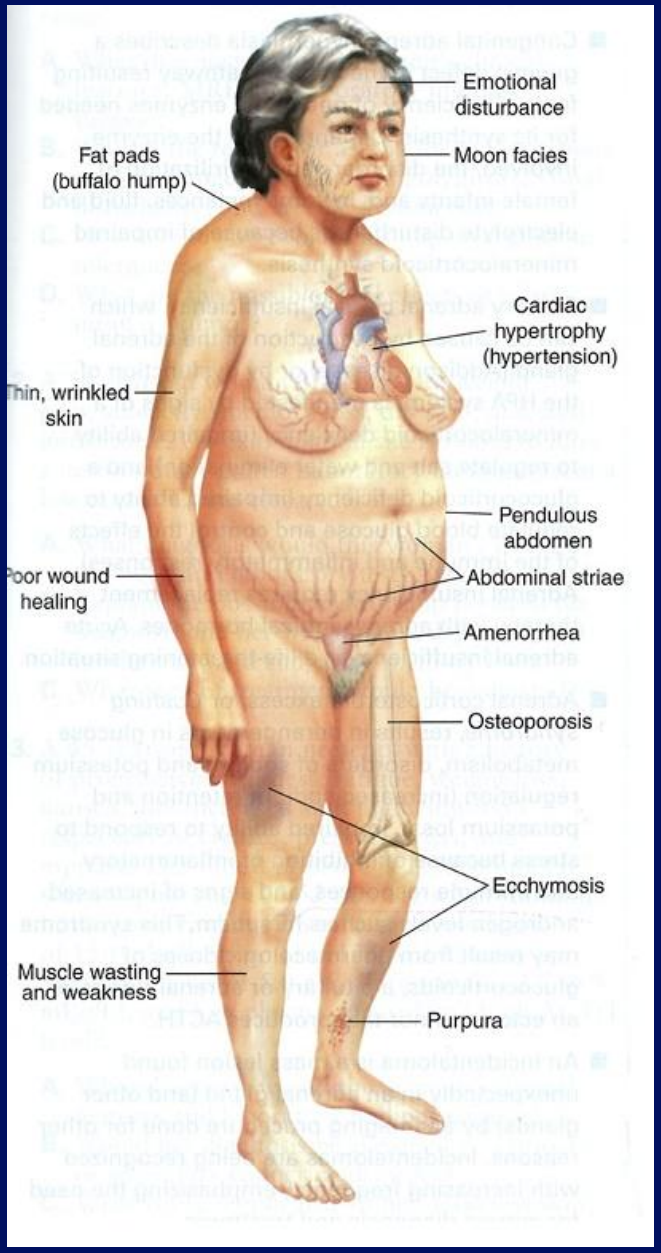
Female patient with hirsutism (Porth, 2014)



Porth, 2014

Cushing´s disease

- CNS: mood swings (depression – euphoria)
- Face: facies lunata, akné, hirsutism – facial hair in androgen sensitive area
- Buffalo hump – fat accumulation
- CVS: art. Hypertension, cardiac hypertrophy
- Metabolism: catabolism, insulin resistance – steroidal diabetes mellitus
- GIT: ulcers
- Amenorea
- Osteoporosis – Ca resorbption
- Muscle catabolism
- Skin: purple striae (mainly on abdomen), ecchymoses, purpura, delayed wound healing, thin skin, fragile vessels



Porth, 2014

Cushing´s syndrome or disease??

- Do not confuse the terms

- Cushing´s syndrome – a syndrome caused by increased levels of cortisol in plasma
- Causes:
  - adrenal adenoma - primary, peripheral disease
  - Iatrogenic cushing syndrome– due to long-term corticosteroids administration – strong antiinflammatory and immunosuppresive drugs
    - To treat chronic inflammatory diseases, degenerative processes; a commom cause of Cushing syndrome
  - Hyperproduction of CRH – rare
  - paraneoplastic
- Cushing´s disease: adenoma producing ACTH (a secondary, central disease)

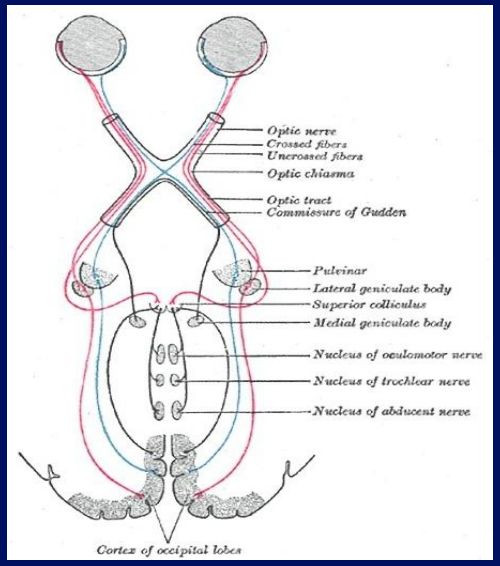
Other adenomas

- d) adenoma producing TSH: hyperplasia of thyroid gland (diffuse goiter), manifestation – central hyperthyreosis

- E) adenoma producing gonadotropins: usually produse inefficient forms of FSH and LH
  - If yes – production is continous (not pulse)
  - Manifestation: central amenorea
  - Pathomechanism: inhibition of GnRH in hypothalamus

Expansive processes in sella turcica

Usually tumors cause compression to chiasma opticum – leading to visual imapriment



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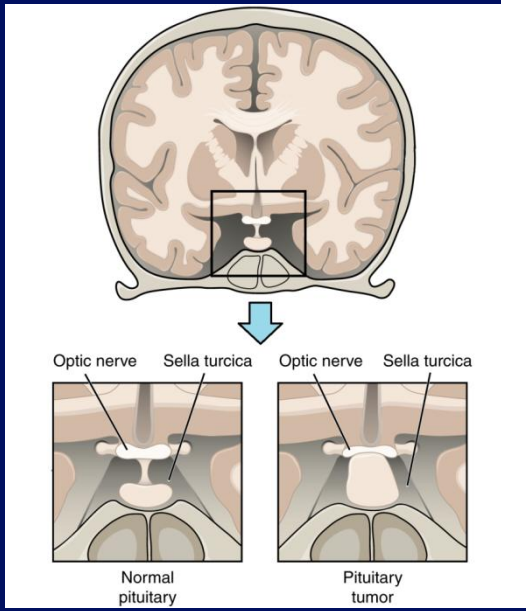

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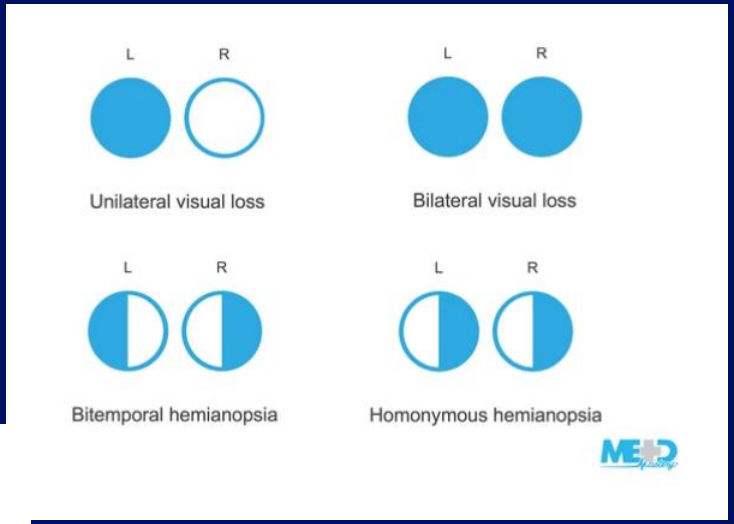

Recognizing pituitary tumors | Medmastery

2. Hypopituitarism

- Decreased production of several pituitary hormones, usually all hormones are affected – panhypopituitarism
- Accompanied by decreased levels of peripheral glands hormones

- Etiology: tumor (pressure), trauma, ischemia, hemorrhage, after surgical operation of pituitary tumors
- Disconnection between hypothalamus and pituitary gland – loss of stimulatory effect of hypothalamic liberins – except of prolactin
  - Prolactin synthesis is increased after disconnection between hypothalamus and pituitary gland – loss of inhibitory effect od dopamin

2. Hypopituitarism

- Sudden damage to the pituitary gland:
  - Deficiency of ACTH and ADH – dangerous state – circulatory colaps, decreased body resistance
  - Decreased TSH, GH, FSH, LH – not life-threatening, but decreased function of relevant glands

2. Hypopituitarism

- Clinical signs: derived from decreased function of peripheral endocrine glands that are driven by relevant pituitary hormones

- Lack of :
  - growth hormone - pituitary nanism
  - TSH - hypothyroidism
  - FSH, LH –hypogonadism
  - ACTH – insufficient body response to stress burden
- Other: decreased cardiac contractility, muscle weakness, decreased bone density (Simmonds cachexy)hypoglycemia, hypercholesterolemia

2. Hypopituitarism

- Sheehan syndrome: sudden onset of hypopituitarism after the labour, acute condition

- Pathomechanism: during pregnancy the pituitary gland physiologically hypertrofies – increased metabolism – increased oxygen demands
- After labour – large loss of blood - arterial hypotension – metabolic needs are suddenly not met - acute pituitary necrosis

Neurohypophysis
Disorders of pituitary gland

Neurohypophysis

- Composed of nerve axons from *ncl.paraventricularis* and *ncl. supraopticus hypotalami*
- Axonal terminals store 2 hormones:
  - vasopressin (ADH),
  - oxytocin
- Their rescretion is regualted by hypothalamus

Disorders of neurohypophysis

- Diabetes insipidus : previously discussed
- SIADH (Schwartz-Bartter syndrome)
- Disorders of oxytocin
  - Hyposecretion
  - hypersecretion

SIADH

- Increased synthesis of ADH

- Etiology: tumors producing ADH, brain damage
- Pathomechanism: Water retention – hyponatriemia
- Also activation of ANP – prevents edema formation
- Clinical signs: lethargy, weakness, confusion, coma, myoclonus, asterixis, cramps

Oxytocin pathologies

- Hyposecretion:
  - a rare condition
  - decreased uterine contraction and milk ejection during the birthing process.
  - Ethiology: Panhypopituitarism
- Hypersecretion
  - a very rare situation
  - overactive uterus, causing hypertrophy and limiting pregnancy due to insufficient space to hold the fetus.

Oxytocin pathologies

- Oxytocin levels have been correlated with mental disorders such as autism, schizophrenia, personality disorders, mood, and eating disorders (Florea, et al. 2022)

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