General principles of endocrine physiology

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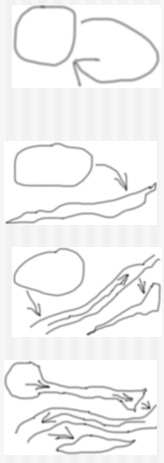
Types of humoral signalization

- Autocrine
  - neighboring cells of the same type or the secreting cell itself (e.g. growth factors)
- Paracrine
  - neighboring cells of different types (e.g. cytokines, neurotransmitters)
- Endocrine
  - from gland via blood to a distance
- Neurocrine
  - via axonal transport and then via blood (oxytocin, ADH, catecholamines)

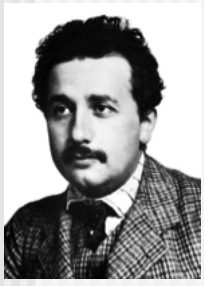


Regulation of homeostasis (*milieu intérieur*)

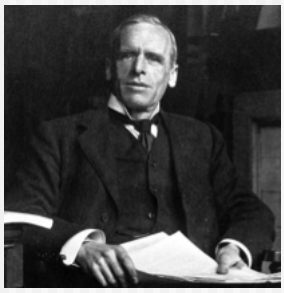
- Nerves
  - fast
  - governing

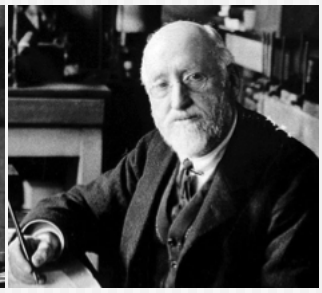
- Hormones
  - mainly metabolism, growth, differentiation, reproduction

(1902 -) 1905



$E = mc^2$





- **Bayliss WM, and Starling EH**. The mechanism of pancreatic secretion. *J Physiol* 28: 325-353, 1902.
- Prestigious Croonian lecture to the Royal Society of Physicians in London, on June 20, 1905
  - **ὁρμάω** (I arouse, activate, stimulate)

Hormone (ὁρμάω)

- Substance produced by a specific cell type usually accumulated in one (small) organ
- Transport by blood to target tissues
  "…chemical messengers which speeding from cell to cell along the blood stream, may coordinate the activities and growth of different parts of the body and the continually recurring physiological needs of the organism must determine their repeated production and circulation from the body" (Starling 1905)
- Stereotypical response (receptors)

Hormone production: "Classic" glands

Hypothalamus:
- GHRH, CRH, TRH, GnRH
- Somatostatin

Pituitary:
- Growth hormone
- Prolactin
- ACTH, MSH
- TSH
- FSH a LH
- Oxytocin
- ADH

Pancreas:
- Insulin
- Glucagon

Gonads:
- Estrogens+progesterone /Testosterone

Epiphysis:
- Melatonin

Thyroid gland:
- T_3, T_4
- Calcitonin

Parathyroid glands:
- Parathormone

Adrenal cortex:
- Cortisol
- Aldosterone
- Androgens

Adrenal medulla:
- Catecholamines

Hormone production: Less traditional sources

Endothelium:
- Endothelins
- NO
- Prostanoids,...

Immune system:
- Cytokines

Platelets, mesenchyme:
- Growth factors

Placenta:
- all hormones

Adipocytes:
- Leptin,...

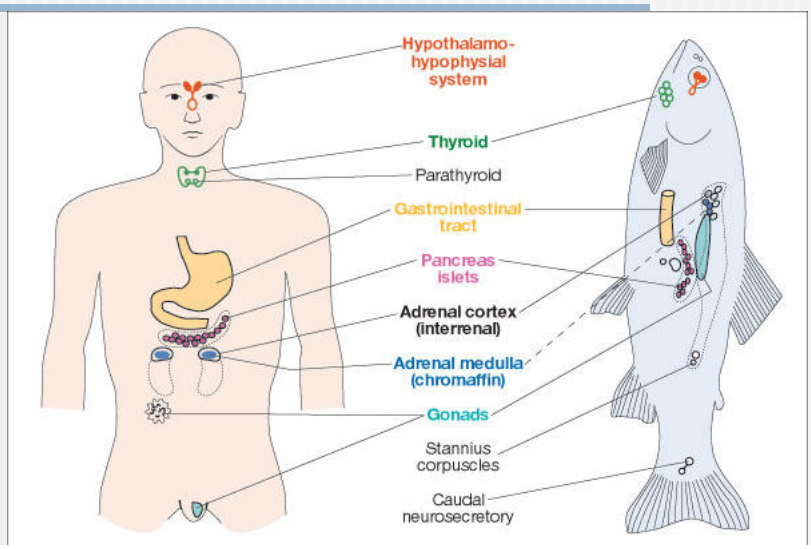
Cardiocytes:
- ANP

Kidney:
- Erythropoietin
- Renin

GIT:
- Gastrin
- Cholecystokinin
- Secretin,...

Gonads:
- Inhibins
- Activins

Hormones are rather conserved in evolution



Hormones, cytokines, growth factors

- Common aspects:
  - small quantities
  - regulate other cells
  - act through receptors
- Tight interactions between immune and endocrine systems

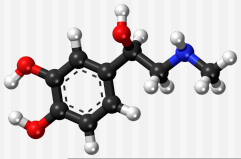
	Hormones	Cytokines	Growth factors
Production	Only specialized cells	Many cell types	
	Few places	Many places	
Action	Long-range	Mostly short-range	Short-range
Pleiotropy	Low	High	Medium
Redundance	Low	High	Medium
Regulation	Tight	Loose	
Function	Homeostasis Ontogenesis	Defence	Remodeling

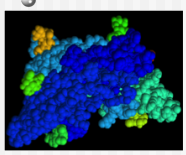
Endocrine and nervous systems

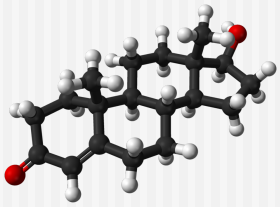
- Many common aspects:
  - small quantities
  - regulate other cells & tissues
  - act through receptors
  - functional overlap between some hormones & neurotransmitters
    - catecholamines, gastrin,…
  - excitability
  - both can secrete into blood

Chemical characteristics of hormones

- Amines (from tyrosine)
  - hydroxylation - catecholamines
  - iodination - thyroid hormones
- Peptides/proteins
  - 3-200 aa residues (TRH – FSH)
- Steroids (from cholesterol)
  - adrenocorticoids
  - sex hormones
  - active metabolites of vitamin D







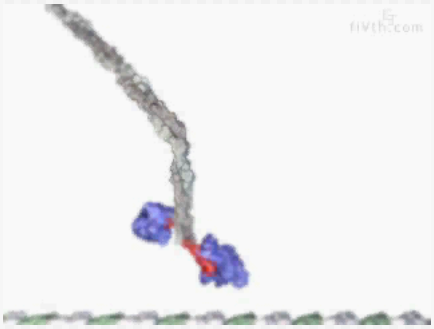
Genetic disorders

- Peptides/proteins:
  - Often gene coding the hormone
    → ↓ activity (e.g. insulin)
- Amines & steroids:
  - gene coding enzyme catalyzing the synthesis
    → ↓ hormone level
    and/or ↑ precursor level
    e.g. ↑ androgens in deficient estrogen synthesis

Hormone release

Proteins & catecholamines:

- secretory granules, exocytosis
  - for incorporation into granules often special sequences cleaved off in granules or after release
  - stimulus →
    ↑ $[Ca^{2+}]_i$ (influx, reticulum)
    → granules travel along microtubules towards cell membrane (kinesins, myosins)
    → fusion

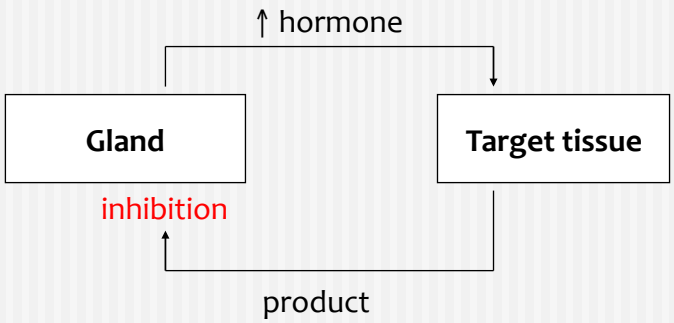


Hormone release

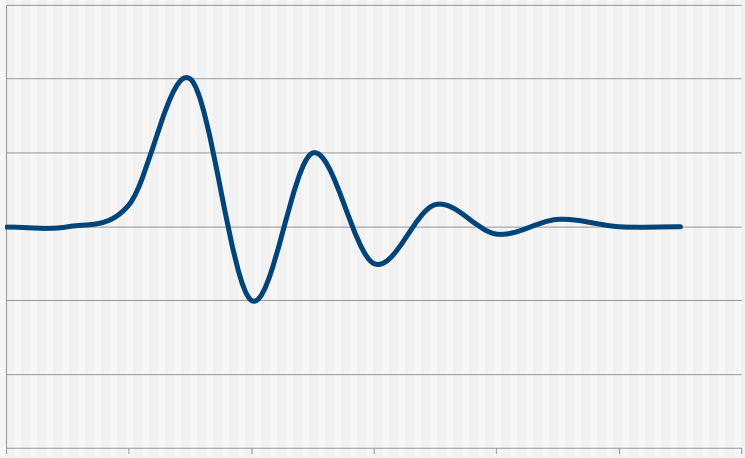
- Thyroid hormones:
  - made as part of thyroglobulin
  - stored in folicles
  - T3 & T4 secreted by enzymatic cleavage
- Steroid hormones:
  - leave the cell across cell membrane right after synthesis (no storage)

Regulation of hormone release

- Feedback
  - Negative

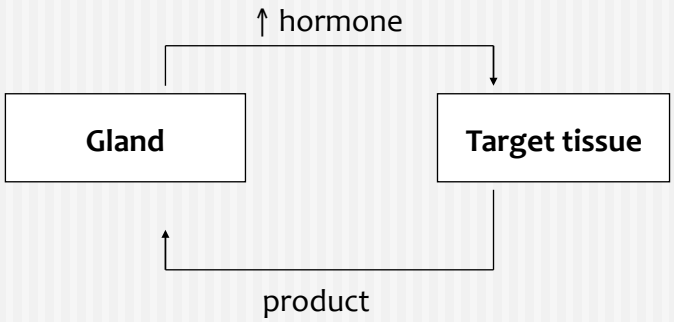


Negative feedback

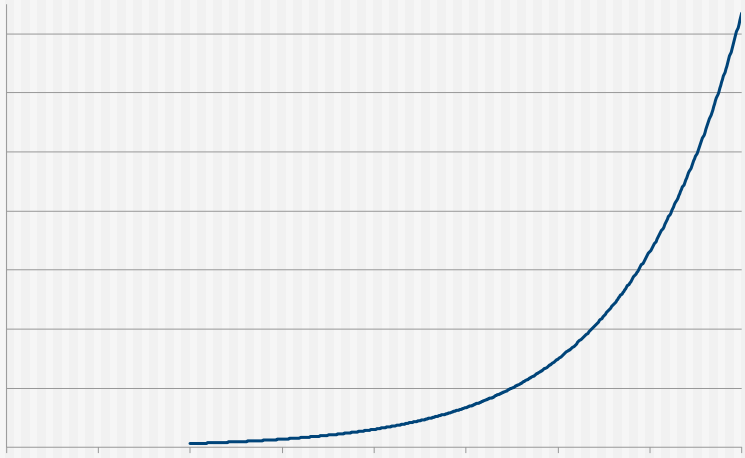


Regulation of hormone release

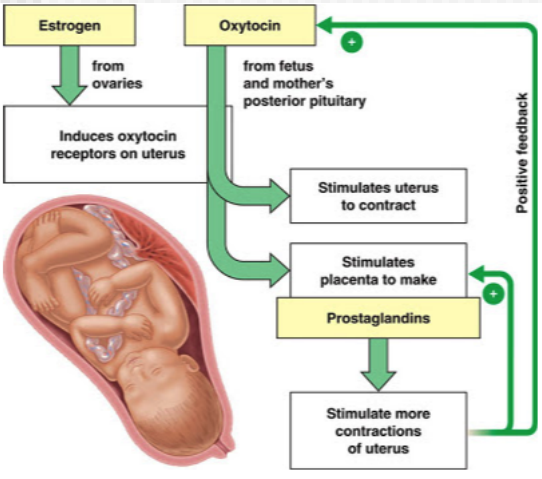
- Feedback
  - Negative
  - Positive (only narrow dose range)

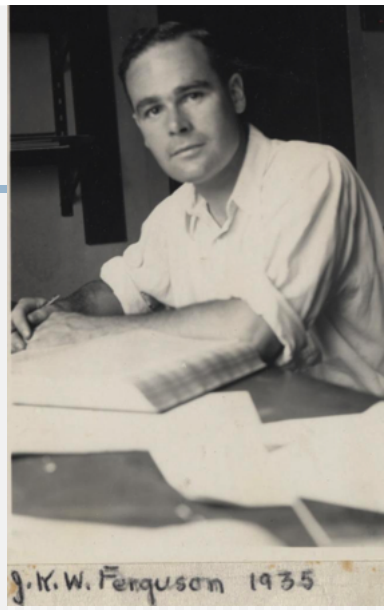


Positive feedback



Ferguson reflex



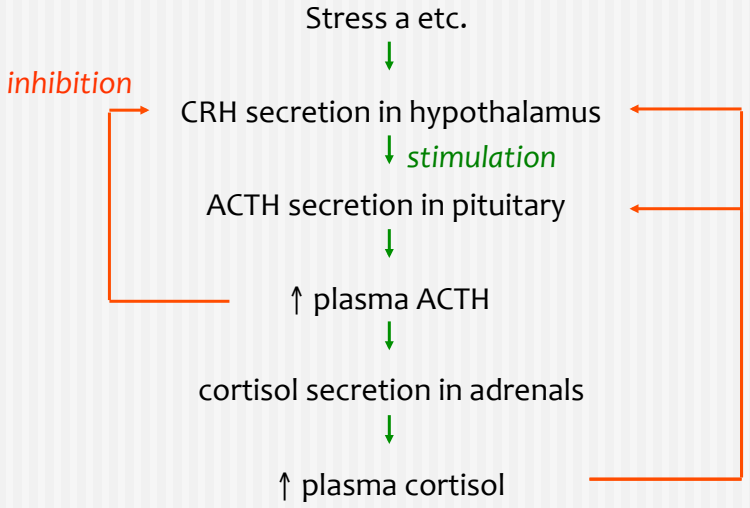


Ferguson, J.K.W.: A study of the motility of the intact uterus at term. *Surg Gynecol Obstet*. 73: 359-66, 1941

Regulation of hormone release

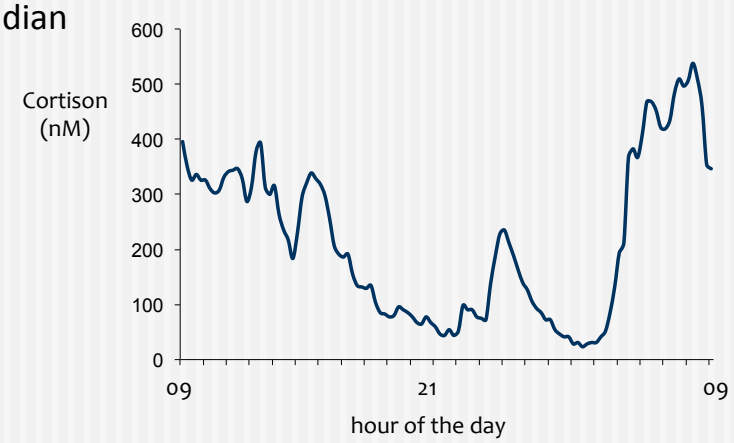
- Feedback
  - Negative
  - Positive (only narrow dose range)
- Nerve regulation
  - pain, emotions, sex, injury, stress,...
  - e.g. ↑ oxytocin with myometrial distension or nipple stimulation (lactation)

Combined feedback



Regulation of hormone release

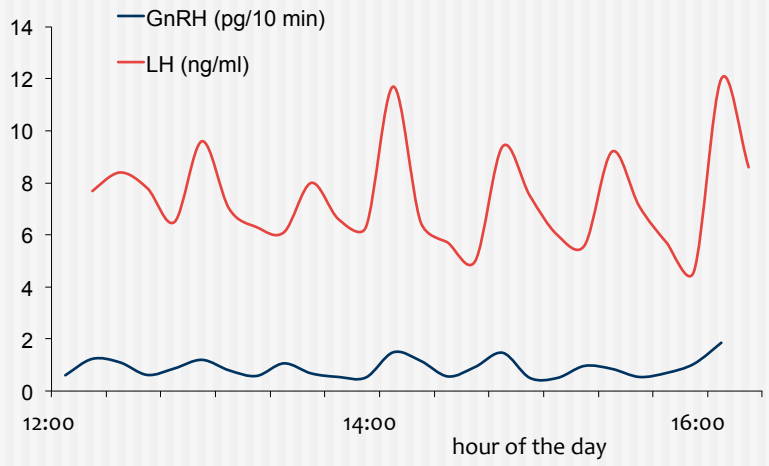
- Rhythms
  - circadian



Regulation of hormone release

- Rhythms
  - circadian
    - light/dark fine/tune endogenous rhythm of cells & suprachiasmatic nucleus of hypothalamus
    - melatonin, cortisol
  - monthly
  - seasonal (day length; atavistic)
  - developmental (puberty, menopause)
- Pulsations/oscillations
  - gonadotropins

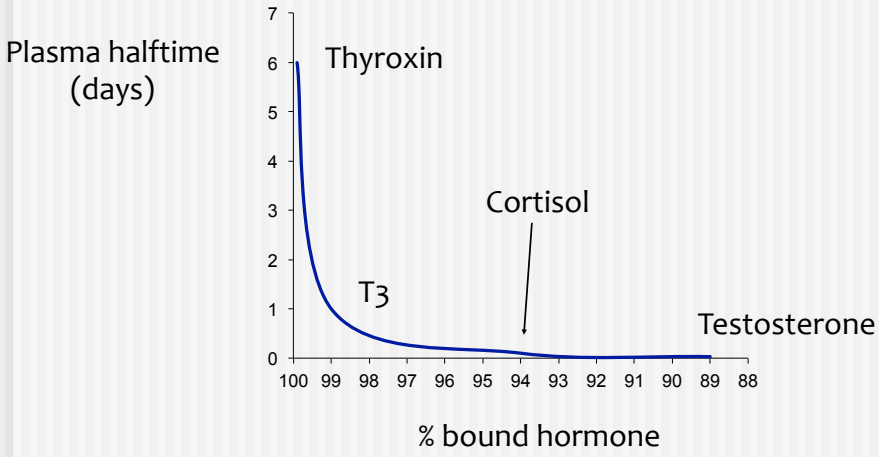
Pulsatility in GnRH & LH release



Transport of hormones

- Freely in blood:
  - Catecholamines
  - Most peptides
- Nonspecific (albumin) and specific transport globulins (from liver):
  - Steroids
  - Thyroid hormones

Transporter binding lengthens hormone halftime



Hormone action

- Receptor
  - specificity of a response to a given hormone
- (Second messenger)
- Δ activity or concentration of enzymes, transcription factors, or structural proteins

Hormone action

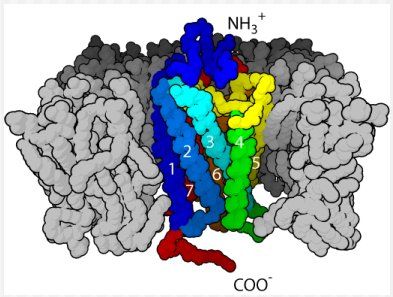
Peptides/proteins Catecholamines	Steroid & thyroid hormones
Receptor in cell membrane	Receptor in cytosol or nucleus
Second messengers → Δ protein activity	Δ gene expression
Fast	Slower

Receptors

- Δ affinity or expression modulates hormone action
  - e.g. phosphorylation, pH, osmolarity,...
- down-regulation
- up-regulation

Membrane receptors

- Large glycoproteins, often several subunits
- Typically 7x through membrane



- After activation:
  - dissociation from the hormone
  - or endocytosis of the complex, then degradation in lysozomes, recycling

G proteins

- α subunit binds activated receptor
- releases GDP, binds GTP
- dissociates from its β subunit & the receptor
- binds & activates/inhibits effector (adenyl/guanylate cyclase, phospholipase C)
- hydrolyzes GTP to GDP
- re-associates with its β-γ dimer

Intracellular signal transduction (second messengers)

- cAMP
- cGMP
- IP_3
- Ca/calmodulin
- tyr kinases
- Smad
- MAP kinases

One hormone can use several systems (in various cells or for different functions)

Adenylate cyclase - cAMP - protein kinase A

- PKA phosphorylates target enzymes (in/activation)
- sometimes complementary (e.g. Ca channel activation + Ca pump inhibition)
- can affect gene expression
  - cAMP regulatory element (CRE) on DNA binds transcription factor, CRE binding protein (CREB)
- cAMP hydrolysis: phosphodiesterases

Ca-calmodulin

- G proteins activate Ca channels (ROC)
- Ca influx stimulates Ca release from endoplasmic reticulum (CICR)
- Ca, mainly by binding calmodulin, modulates many enzymes, often via protein kinase C

Phospholipase C - IP_3 & DAG

- from cell membrane phospholipids
- IP_3 activates Ca channel of the endoplasmic reticulum
- DAG: ↑↑ PKC affinity to Ca

Tyrosin kinases

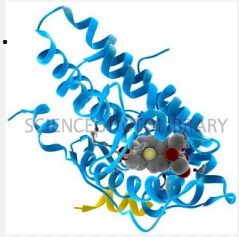
- Receptor autophosphorylation upon hormone binding unmasks tyr-kinase activity
  - typically insulin (& growth factors)
- Or conformational change of the receptor upon hormone binding attracts & activates cytoplasmic tyr-kinases
  - e.g. growth hormone
- tyr-kinases phosphorylate cascades of tyr & ser kinases & phosphatases

Intracellular receptors

- Lipophilic hormones:
  - Thyroid
  - Steroid
  - Vitamin D
- Enter the cell (corticoids) or all the way to nucleus (T3, T4), where they bind the receptor (large oligomeric protein)

Function of intracellular receptors

- Hormone displaces inhibitory protein (e.g. HSP) → translocation to nucleus, DNA binding
  - corticoids



- Or hormone binding displaces the receptor from resting, inhibitory association with DNA
  - thyroid hormones

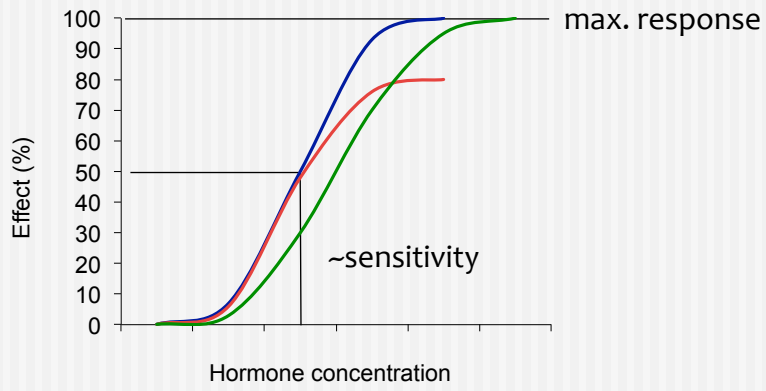
Inactivation of hormones

- Target tissue uptake
- Metabolic degradation (plasma, liver, kidney)
- Excretion in urine
  (↓ by transporter binding; low for proteins - also re-absorbtion & degradation in kidneys)

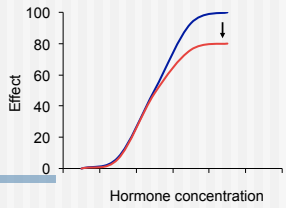
Magnitude of response

- hormone concentration
- number of receptor molecules
- duration of exposure
- intracellular conditions (second messengers, kinases,…)
- synergistic or antagonistic influences

Dose/response curve

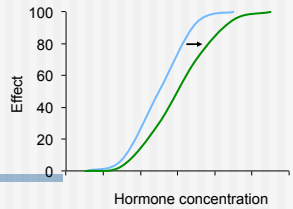


Decrease in max. response



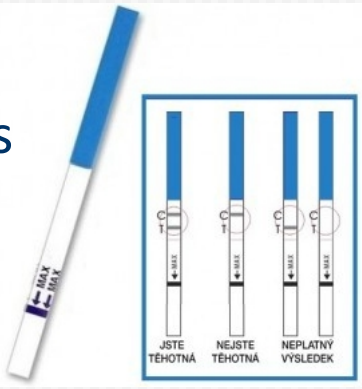
- less receptors
  - less target cells
- less/lower activity of enzymes activated by hormone
- less substrate for final product
- more non-competitive inhibitor

Drop in sensitivity



- lower receptor affinity
- modulating factors
- faster hormone degradation
- competitive inhibition
- more antagonistic hormones

Measuring hormones



- immunoassay (RIA, ELISA,...) (pM)
- Bioassay (biol. activity can differ from concentration or immunoreactivity - e.g. mutation of the gene for the hormone)