General principles of endocrine functions. Hypothalamus. Adenohypophysis. Thyroid gland.

Doc. PharmDr. Petr Babula, Ph.D.

Integration systems of organisms

- Integration and coordination = ensuring the integrity and all activitis (functions) of the organism at all levels as a response to the changing conditions of the external and internal environment

- Hormonal (endocrine) system - **hormones**
- Nervous system - **neurotransmitters**
  - neuroendocrine cells and neuroendocrine integration

- Immune system - **special signal molecules**

- What do nerve and hormonal signals direct and regulate?
  - Metabolism and inner environment of the body (homeostasis)
  - Growth and development
  - Functions of all tissues and organs
  - Reproductive behavior
  - Reactions as a responses to the external environment

Chemical messengers

- **Cytokines**
  - small signaling proteins (especially glycoproteins) - cell communication
  - Extremelly effective (low concentrations)
  - Pleiotropic effect + redundancy
  - *Hematopoietic growth factors, interferons, interleukins, lymphokines, monokines including chemokines, etc.*
- **Chemokines**
  - A group of cytokines (highly homologous proteins) - chemotactic effect
  - Homeostatic processes - cell migration, "maintenance" and development of tissues
  - Inflammatory processes - immune response (chemoattractant effect on leukocytes)
  - Other - eg. tumor (tumor growth, angiogenesis)
- **Neurotransmitters**
  - synthesized in neurons and stored
    - Readily releasable vesicles (1-2%), recycling vesicles (5-20%), reserve vesicles (90%)
    - Approximately 100 substances of various chemical groups
    - Various classification (low- / high molecular weight compounds, excitation / inhibition / modulation, etc.)
- **Hormones**

Hormones

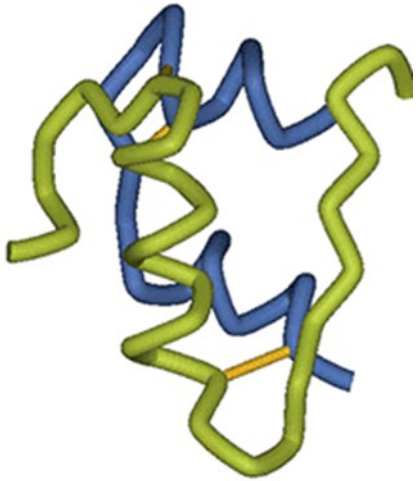
- Starling 1905 – *„secretin“*
- Relatively slow and long-term transmission of signals
- Transport
- Production – cells/tissues/organs
- Glandotropic hormones X aglandotropic hormones
- Target cells
- The short duration of action (usually)

Principles of control of hormonal secretion rates

- **Mechanism of feedback!**
  - Secretion regulated by hormone levels
  - Negative (prevents overactivity of hormone systems)
  - Positive
  - Simple X complex
- Cyclical variations in hormone release
  - (diurnal(daily)/seasonal/annual cycles, ontogenetic development and aging, sleep – example of growth hormone)
- Pleiotropic effect
- Multiplicity of hormone action
- Permissive effect of hormones

Hormones - proteins and peptides

- Majority of hormones
- From small peptides (3 AA – thyrotropin releasing hormone, TRH) to proteins (200 AA – growth hormone)
- Hydrophilic
  - Hormones of hypothalamus and hypophysis
  - Pancreatic hormones - (A (alpha) cells - glucagon, B (beta) cells - insulin, D (delta) cells - somatostatin and PP (gamma) cells - pancreatic polypeptide, 36 AA)
  - Calcitonin, parathyroid hormone, human chorionic gonadotropin, human chorionic somatomammotropin, renin, erythropoietin, natriuretic peptides, gastrin, secretin, cholecystokinin, leptin
  - Sometimes further classified into "families" (or "superfamilies") according to homologous sequences of AAs in primary structure:
    - Insulin group (insulin, IGF I / II, relaxin)
    - The glycoprotein group (LH, FSH, TSH, hCG)
    - Group of growth hormone (RH, PRL)
    - Group of secretin (secretin, glucagon, GIP, glicentin)



Hormones – derivatives of aminoacids (AA) = amine hormones

- Derivatives of amino acids, mainly tyrosine derivatives
  - Catecholamines - adrenalin, noradrenalin, dopamine
  - Lipophilic thyroid hormones - thyroxine, triiodothyronine
- Tryptophan - synthesis of melatonin
- Example: synthesis of thyroid hormones
  - Oxidation of I^- to I^0 (thyreoidal peroxidase)
  - Iodination of thyrosine residues at the position 3 in thyroglobulin (= MIT, monoiodothyronine)
  - Iodination at next position (5) – DIT (diiodothyronine)
  - Oxidative condensation of two DIT molecules = thyroxine (T4)
  - Oxidative condensation of DIT and MIT = triiodothyronine (T3)

Steroid hormones

- Steroid hormones
  - Lipophilic (fat soluble)
  - According to biological activity are classified into groups:
    - Glucocorticoids (cortisol, regulation of metabolism/catabolic effect)
    - Mineralocorticoid (aldosterone, regulation of kalemia/natremia)
    - Androgens (testosterone, sexual development, anabolic effect, hematopoiesis)
    - Estrogens (estradiol, proliferative effect, CNS effects, etc.).
    - Progestins (progesterone, progestogenic and thermogenic effects)
    - 1,25-dihydroxycholecalciferol (intestinal absorption of Ca, bone mineralization)

- Biosynthesis from cholesterol
- Almost no reserves in the producing cells
- Rapid mobilization of cholesterol esters (cytoplasm)
- Sources of cholesterol – plasma, *de novo* biosynthesis in steroid-producing cells
- Simply transport across the cell membrane (lipophilicity)

Comparison of individual types of hormones

Comparison of Peptide, Steroid, and Amino Acid-Derived Hormones — Table 7.1

	Peptide Hormones	Steroid Hormones	Amine Hormones (Tyrosine Derivatives)	
			Catecholamines	Thyroid Hormones
Synthesis and storage	Made in advance; stored in secretory vesicles	Synthesized on demand from precursors	Made in advance; stored in secretory vesicles	Made in advance; precursor stored in secretory vesicles
Release from parent cell	Exocytosis	Simple diffusion	Exocytosis	Simple diffusion
Transport in blood	Dissolved in plasma	Bound to carrier proteins	Dissolved in plasma	Bound to carrier proteins
Half-life	Short	Long	Short	Long
Location of receptor	Cell membrane	Cytoplasm or nucleus; some have membrane receptors also	Cell membrane	Nucleus
Response to receptor-ligand binding	Activation of second messenger systems; may activate genes	Activation of genes for transcription and translation; may have nongenomic actions	Activation of second messenger systems	Activation of genes for transcription and translation
General target response	Modification of existing proteins and induction of new protein synthesis	Induction of new protein synthesis	Modification of existing proteins	Induction of new protein synthesis
Examples	Insulin, parathyroid hormone	Estrogen, androgens, cortisol	Epinephrine, norepinephrine	Thyroxine (T_4)

Silverthorn, D. U. Human Physiology – an Integrated Approach. 6th. edition. Pearson Education, Inc. 2012.

Hormone secretion

- Very low plasma levels – from 1 pg - few mg/ml = very low rates of secretion
- Different secretion rates
  - few seconds after stimulation – very rapid action of hormone
  - the action of other hormones (eg. thyroxine, growth hormone) may require months for full effect
- Each of the different hormones has its own characteristic onset and duration of action
- Regulated neuronally (mediators (substances) in blood, exogenous factors, …)
- Secretion may be continual or cyclical (pulse)
- Different secretion in:
  - Individual phases of the ontogenetically development and aging (childhood, age)
  - Dependence on sex
  - Dependence on vigilance (vigil X sleep)

Transport of hormones

- Strict regulation of hormone concentration in blood
- Role of physico-chemical properties of hormone (lipophilicity, hydrophilicity)
- Generally, very low plasma concentrations (as little as one picogram to few micrograms.ml^{-1})
- Hydrophilic hormones
  - Peptides/proteins, catecholamines
  - Dissolved in blood (blood plasma)
  - Very rapid elimination (MAO, COMT)
- Steroid and thyroid hormones
  - Mainly bound to plasma proteins (albumin, prealbumin, globulins)
  - Only about 10% in the free form
  - Example - Thyroxine - 99% bound, less than 1% in the free form
  - The complex hormone-protein is inactive (inability to achieve the target cell)
  - After dissociation and release of hormone = the active form
  - Complex protein-hormone - storage function „pool", but also protection against degradation = slow elimination

Clearance of hormones, elimination of hormones

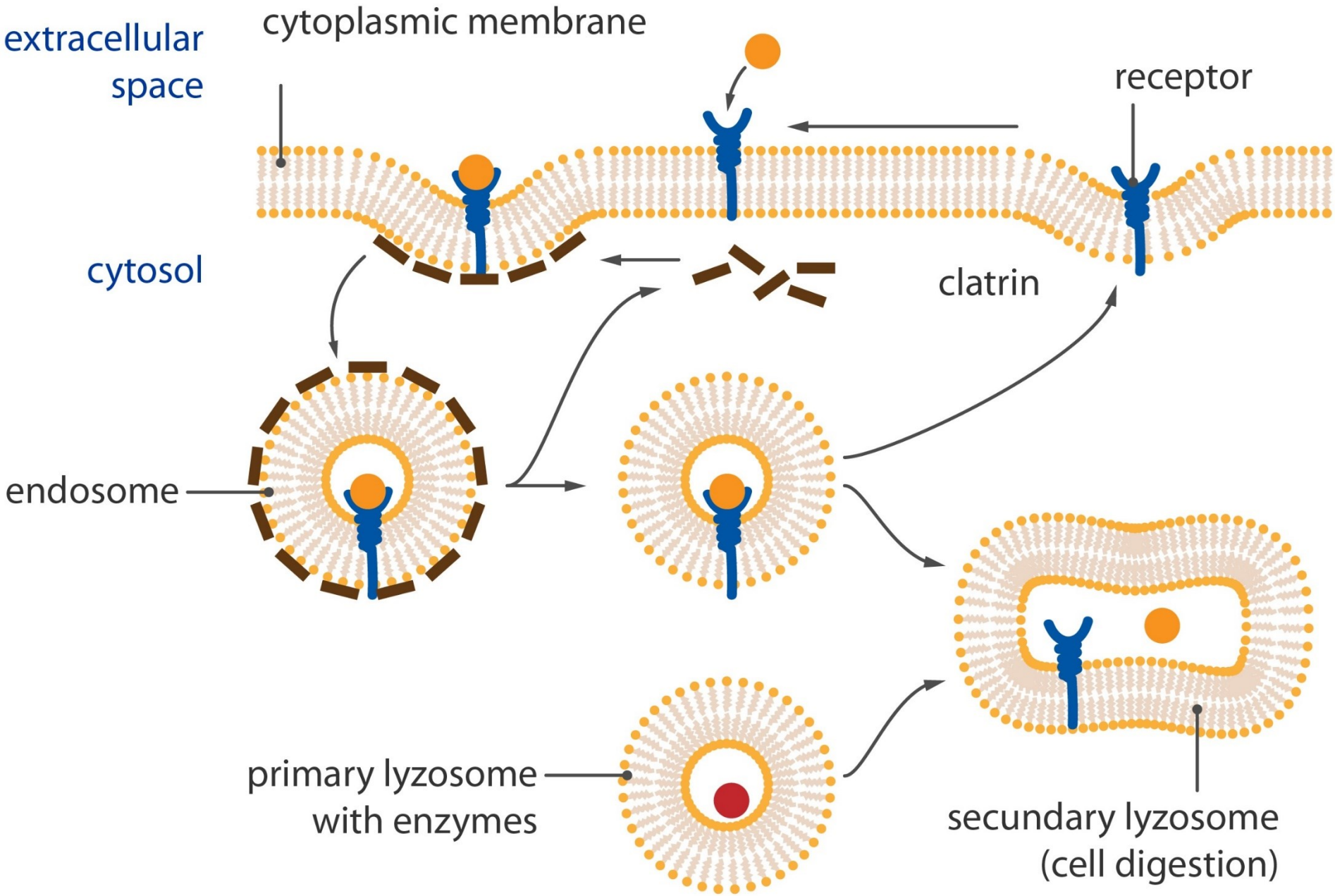
- Metabolic destruction by the target tissues or cells (enzymatically by target cells (complex hormone-receptor, by degrading enzymes present in the blood plasma)
- Binding with the tissue
- Excretion by the liver into bile
- Excretion by the kidneys into urine
- Half-life for angiotensin II circulating in the blood is less than a minute
- Half-life for thyroid hormones may be as long as 1 to six day (they are bound to the proteins)

Effects of hormones

- Endocrine (circulating blood)
- Paracrine - through ECF
- Autocrine
- Neurocrine secretion

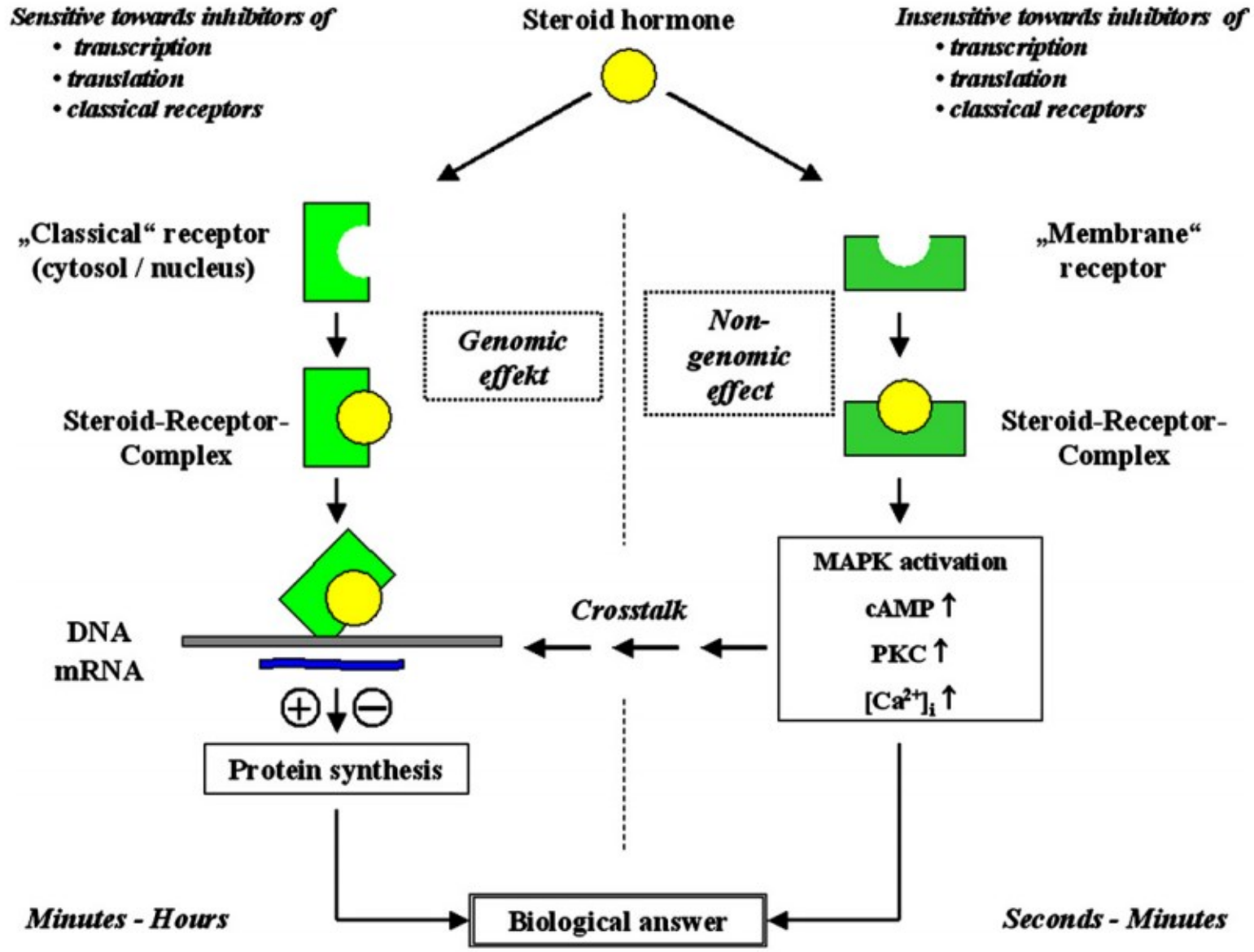
Mechanism of action of hormones

- Receptor of the target cell
- Receptor = protein or glycoprotein structure
- The number and sensitivity of receptors are regulated
  - Changes often already within a few minutes
  - Inactivation / elimination; for example – increased concentration of hormone and increased binding with its target cell receptors may cause the number of active receptors to decrease
  - *Down-regulation*
    - Inactivation of ligands, intracellular signaling molecules, degradation of receptors, decreased production of receptors, eventually other mechanisms
  - *Up-regulation*
    - increased production / availability


extracellular space
cytoplasmic membrane
receptor
cytosol
clatrin
endosome
primary lyzosome with enzymes
secundary lyzosome (cell digestion)

Cytosolic receptors

- Cytosolic – for steroid hormones
- Transport into the nucleus
- Binding of complex with DNA, respectively with the specific regulatory sequence of DNA called HRE promoter sequence (= hormone response element)
- Activation or inactivation of transcription of certain genes
- Note: nongenomic action of steroid hormones
- Note: Aldosterone
  - Aldosterone binds with the receptor in the cytoplasm (mineralocorticoid receptor) of renal tubular cells
  - After about 45 minutes, proteins begin to appear in the renal tubular cells and promotes sodium reabsorption from the tubules and potassium secretion into the tubules
  - The full action is delayed for 45 minutes up to several hours or even hours



Zoellner S, Hwang KH, Wilzewski B, Carapito C, Leize-Wagner E, Van Dorsselaer A, Bernhardt R: **Aldosterone: From biosynthesis to non-genomic action onto the proteome.** ***Steroids 2008, 73(9-10):966-972.***

Nuclear receptors

- Thyroid hormones
- Binding with specific receptors in the nucleus
- After binding - (these receptors act as activated transcription factors localized within the chromatin), which control the function of promoters
- Modification of gene expression of many (more than 100) intracellular proteins, many of them controls / regulates the intracellular metabolic activity
- Once bound to the intranuclear receptors, the thyroid hormones can continue to express their control functions for days or even weeks

Membrane receptors

- Hydrophilic hormones
- Ionotropic X metabotropic
- The biological effect is mediated by:
  - Affecting of ion channels (eg. acetylcholine, adrenaline)
  - G protein-linked receptors
    - Of more than 1000 known G protein-linked receptors
    - transmembrane segments
    - G proteins three parts – a, b, and g
    - Conformational change
    - GDP for GTP = dissociation of a subunit
    - Interaction of a subunit with target molecules
    - Changes in many processes, changes in enzyme activities (adenylyl cyclase, phospholipase C) = alterations in cell functions
    - Inactive state (GDP) / active state (GTP)
    - Gi (inhibitory G proteins) versus Gs (stimulatory G proteins)

Enzyme-linked hormone receptors

- **Receptors with direct/indirect enzymatic activity**
- Structure
- Activation after the binding of the ligand (very rarely inactivation)
- Example – leptin receptor
  - Member of a family of cytokine receptors
  - Associated with enzyme – tyrosine kinase of the janus kinase (JAK) family
  - Dimeric
  - After binding - change in conformation - phosphorylation and activation of JAK2-associated molecules
  - JAK2 molecules then phosphorylate other tyrosine residues in the leptin-receptor complex and mediate intracellular signaling
  - Activation = phosphorylation of STAT proteins + activation of MAPK (mitogen-activated protein kinases) and PI3K (phosphatidylinositol 3-kinase)
- Another example – receptors that activate adenylyl cyclase, which catalyzes the formation of cAMP with multiple effects within the cells
- Atrial natriuretic peptide (ANP) – cGMP is the second messenger

Enzymes-linked hormone receptors

- Tyrosine kinases
  - Receptor tyrosine kinase
    - **When activated, intrinsic tyrosine kinase activity phosphorylates itself and other proteins**
      - Monomeric – for example receptors for Nerve growth factor (NGF), Epidermal growth factor – after ligand binding the receptor dimerizes with activation of intrinsic tyrosine kinase activity and phosphorylation of tyrosine moieties on itself and other proteins, which causes biological response
      - Dimeric – for example receptors for insulin and IGF – binding of ligand activates intrinsic tyrosine kinase activity and leads to the phosphorylation of itself and other proteins
  - Tyrosine kinase-associated receptors
    - Intracellular domain without tyrosine kinase activity, but is **non-covalently associated with enzyme with tyrosine kinase activity (JAK)**
    - Activation of JAK = phosphorylation of both receptor and other target proteins

Adenylyl cyclase- cAMP system

- Gs/Gi proteins
- After exchange of GDP for GTP, the dissociation of a subunit with GTP from the trimeric complex follows. Complex a subunit-GTP activates adenylyl cyclase at the inner membrane, which leads to an increase in cAMP level in the cell (Gs) or to decrease in cAMP in the cell (Gi, inhibition)
- Hormones that activate Gs: ACTH, ADH, adrenaline, noradrenaline, calcitonin, CGRP, CRH, dopamine, FSH, glucagon, oxytocin, secretin, and some other
- Gi activates the some hormones, but also acetylcholine, angiotensin II, dopamine, melatonin, somatostatin, and some others
- cAMP subsequently activates protein kinases of the A type (PKA)
- Prosphorylation of proteins
- There are also interferences with other kinases
- Regulatory role of alpha subunit, cleavage of GTP to GDP and Pi and creation of trimeric structure of G protein.
- Inactivation of cAMP by phosphodiesterase (catalyzes creation of 5´-AMP)
- Inactivation by phosphatases

IP3 and DAG as second messengers

- angiotensin II, GnRH, some catecholamines, oxytocin, GHRH, TRH, vasopressin
- PIP2, phosphatidylinositol-4,5-bisphosphate, a minor phospholipid of plasma membrane
- two products, IP3 (inositol triphosphate) and DAG (diacylglycerol)
- IP3 mobilizes calcium ions from mitochondria and endoplasmic reticulum
- calcium ions = next messenger molecules (contraction of smooth muscle, secretory function)
- DAG activates protein kinase C = cell response.

Calcium-calmodulin system

- The system based on the entry of calcium ions into the cell, which can be induced:
  - By changing the membrane potential that leads to the opening of calcium channels
  - Receptor that is linked with calcium channel
  - „Normal“ concentration of free intracellular calcium ions varies from 10^{-8} to 10^{-7} $mol.L^{-1}$;
  - When the concentration of calcium ions rises to 10^{-6} to 10^{-5} $mol.L^{-1,}$ enough binding occurs to cause intracellular actions of calmodulin
- Calcium ions bind to calmodulin upon entry

NO as a signal molecule

- NO - nitrergic neurons, endothelium
- NO synthase (NOS)
- Activation of NOS = Ca^{2+}-calmodulin system
- NO diffuses very rapidly into cells
- Activation of cytoplasmic guanylate cyclase
- Creation of cGMP, which serves as a second messenger and activates protein kinase G.
- Protein kinase G causes changes in free intracellular calcium ions with subsequent vasodilatation.
- Application in therapy – inhibition of cGMP-specific phosphodiesterase, prolonged vasodilatation (Viagra)

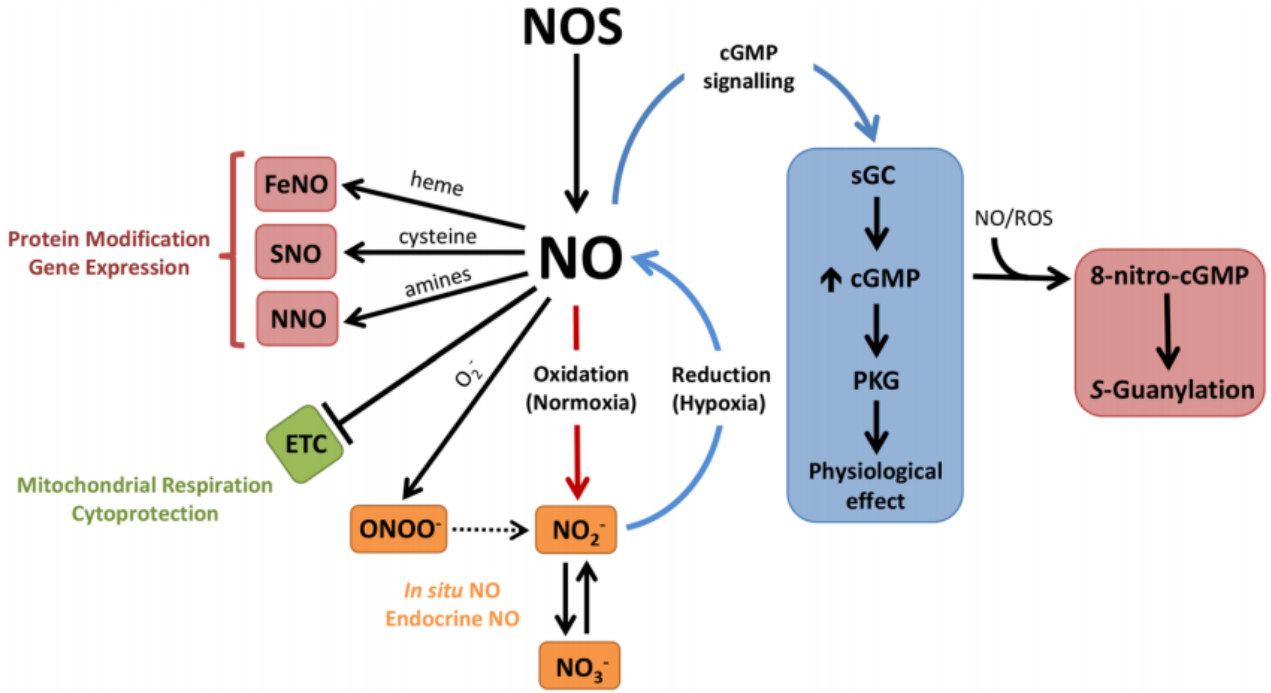


Fig. 1 Synthesis and fate of nitric oxide (NO) in vivo. Nitric oxide synthase enzymes (NOS1, NOS2 and NOS3) catalyse NO formation from L-arginine and O_2. NO signalling can occur proximate to the site of production by binding to soluble GC (sGC) which triggers a rise in the second messenger cyclic GMP (cGMP), activating protein kinase G (PKG) and thus inducing a physiological effect. NO and metabolites can interact with cGMP to form 8-nitro-cGMP that regulates proteins via *S*-guanylation. The major path for NO metabolism is via oxidation to nitrite (NO_2^-) and nitrate (NO_3^-), which may proceed via autooxidation or be catalysed by a number of factors (see supplementary Fig. S1). During hypoxia and/or acidosis, NO_3^- can be reduced to NO_2^- and NO, a process that is O_2 independent. NO reacts with superoxide (O_2^-) to form the radical oxygen species (ROS) peroxynitrite ($ONOO^-$). Flux between $ONOO^-$ and NO_2^- has been suggested as a major route for NO_2^- formation. NO can interact with components of the mitochondrial electron transport chain (ETC) to interrupt electron flow and, therefore, respiration, and reduce ROS damage. Superoxide and hydrogen peroxide (H_2O_2) generated by complex I and III can irreversibly bind the heme moiety of complex I and IV. However, NO excludes ROS interactions with the heme moeity due to its higher affinity for the binding site. The regulation of gene expression and protein function can be altered by nitrosylation through the addition of a nitrosyl ion (NO^-) to a metal (i.e. iron) to form iron-nitrosyl (FeNO) compounds, or to a thiol to form *S*-nitroso (SNO) compounds. Similarly, nitrosation through the addition of a nitrosonium ion (NO^+) to various amines can form *N*-nitroso (NNO) compounds. Modified from Martinez-Ruiz et al. (2011)

Donald JA, Forgan LG, Cameron MS: **The evolution of nitric oxide signalling in vertebrate blood vessels.** ***J Comp Physiol B-Biochem Syst Environ Physiol 2015, 185(2):153-171.***

Measurement of levels of hormones in the blood

- Problem = extremely low levels of hormones in the blood
- Highly sensitive methods, such as radioimmune assay
  - Extremely sensitive and specific
  - Firstly used for quantification of insulin (fifties of 20th century)
  - Rosalyn Sussman Yalow won the Nobel Prize in medicine in 1977 for this method
  - Principle: immunochemical reaction between antigen and antibody carried out *in vitro* in the presence of suitable radioindicator
  - Distribution of radioindicator is monitored and quantified
  - Very expensive method
- ELISA
  - Interaction antigen-antibody
  - ELISA at different arrangement (direct/indirect)

Hierarchy of hormones

- 1. Nerve signal in CNS
- 2. Neurohormonal "switching" center = hypothalamus
- 3. Release of the hormone – hypothalamus and neuronally associated neurohypophysis or secondarily from the anterior pituitary – adenohypophysis
- 4. Glandotropic hormones of adenohypophyse control periperal endocrine glands that secrete hormone(s)
- 5. Superior hormones also influence the growth of peripheral endocrine glands (compensatory hypertrophy, compensation atrophy)
- The possibility of multiple modulation / signal amplification
- Hormones independent of the hypothalamus-hypophysis axis:
  - Pancreatic hormones
  - Parathyroid hormone, calcitonin and calcitriol
  - Angiotensin and aldosteron
  - Erythropoietin
  - Hormones produced in GIT
  - Atrial natriuretic hormone
  - Melatonin

Hypothalamus-hypophysis system

- Hypothalamus
  - Section of the anterior part of diencephalon, located under *sulcus hypothalamicus* and in front of interpedunclular nuclei
  - Connected with neurohypophysis via bundle of nerve fibers (*ncl. supraopticus* and *ncl. supraventricularis*)
  - The connection with adenohypophysis is mediated via vessels (pituitary portal vessels), an integral part of hypophyseal portal system
  - Arterial branches of the carotid arteries and *circulus Willisi* form on the ventral side of the hypothalamus a network of fenestrated capillaries - the primary capillary plexus
  - The capillaries are connected into the sinuses that as hypophyseal portal veins transport the blood through the pituitary stalk to the capillaries of anterior pituitary – adenohypophysis
  - Short portal circulation connects adenohypophysis and neurohypophysis

Functions of hypothalamus

- Sleep and vigil and relation to biological rhythms
- Regulation of body temperature
- Vegetative functions, emotions and behaviors
- Appetitive behavior (hunger, thirst)
- Sexual behavior / sexual orientation?
- **Endocrine functions**:
  - AH is fundamentally regulated (excepting PRL) by production of **inhibitory/stimulatory hormones for adenohypophysis** that are synthesized in various **hypothalamic nuclei**
  - After release from nerve terminations are transported via portal circulation indo adenohypophysis, where stimulate or inhibit production and secretion of corresponding adenohypophyseal hormones
  - Hypothalamus **directly synthesizes hormones for neurohypophysis** (vasopressin (ADH), oxytocin; supraoptic and paraventricular nuclei); magnocellular neurons, axonal transport to the neurohypophysis
- Hypothalamus gathers information about:
  - Concentration of nutrients, electrolytes and hormones
  - osmolarity of blood
  - From sensoric system
  - About global functions
- Based on the information, hypothalamus affects function of hypophysis

TABLE 18–1 Summary of principal hypothalamic regulatory mechanisms.

Function	Afferents from	Integrating Areas
Temperature regulation	Temperature receptors in the skin, deep tissues, spinal cord, hypothalamus, and other parts of the brain	Anterior hypothalamus, response to heat; posterior hypothalamus, response to cold
Neuroendocrine control of:		
Catecholamines	Limbic areas concerned with emotion	Dorsal and posterior hypothalamus
Vasopressin	Osmoreceptors, "volume receptors," others	Supraoptic and paraventricular nuclei
Oxytocin	Touch receptors in breast, uterus, genitalia	Supraoptic and paraventricular nuclei
Thyroid-stimulating hormone (thyrotropin, TSH) via TRH	Temperature receptors in infants, perhaps others	Paraventricular nuclei and neighboring areas
Adrenocorticotropic hormone (ACTH) and β-lipotropin (β-LPH) via CRH	Limbic system (emotional stimuli); reticular formation ("systemic" stimuli); hypothalamic and anterior pituitary cells sensitive to circulating blood cortisol level; suprachiasmatic nuclei (diurnal rhythm)	Paraventricular nuclei
Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) via GnRH	Hypothalamic cells sensitive to estrogens, eyes, touch receptors in skin and genitalia of reflex ovulating species	Preoptic area; other areas
Prolactin via PIH and PRH	Touch receptors in breasts, other unknown receptors	Arcuate nucleus; other areas (hypothalamus inhibits secretion)
Growth hormone via somatostatin and GRH	Unknown receptors	Periventricular nucleus, arcuate nucleus
"Appetitive" behavior		
Thirst	Osmoreceptors, probably located in the organum vasculosum of the lamina terminalis; angiotensin II uptake in the subfornical organ	Lateral superior hypothalamus
Hunger	Glucostat cells sensitive to rate of glucose utilization; leptin receptors; receptors for other polypeptides	Ventromedial, arcuate, and paraventricular nuclei; lateral hypothalamus
Sexual behavior	Cells sensitive to circulating estrogen and androgen, others	Anterior ventral hypothalamus plus, in the male, piriform cortex
Defensive reactions (fear, rage)	Sense organs and neocortex, paths unknown	Diffuse, in limbic system and hypothalamus
Control of body rhythms	Retina via retinohypothalamic fibers	Suprachiasmatic nuclei

Stimulatory and inhibitory hormones of hypothalamus – „releasing“ and „inhibiting“ hormones of hypothalamus

- TRH
  - parvocellular part of *nucleus paraventricularis*
  - synthesis regulated by hormones of thyroid gland (negative feedback)
  - synthesized in other parts of the CNS as well as outside the CNS (cardiovascular system, GIT)
  - positive inotropic and chronotropic effect on the myocardium, affects signal transmission in CNS, increases vigilance, stimulates respiration.
- CRH
  - stimulates synthesis of POMC (pro-opiomelanocortin, a precursor protein)
  - parvocellular part of hypothalamic *nucleus paraventricularis*
- GHRH – *nucleus arcuatus*.
- GHIH –
  - also important neurotransmitter in spinal cord, brain stem and cortex
  - GIT – inhibition of secretion of GIT hormones
- GnRH
  - paraventricular area of hypothalamus (*nucleus arcuatus)*, and from medial preoptic area.
- PIH – dopamine.

Hypothalamic Releasing and Inhibitory Hormones That Control Secretion of the Anterior Pituitary Gland

Hormone	Structure	Primary Action on Anterior Pituitary
Thyrotropin-releasing hormone (TRH)	Peptide of 3 amino acids	Stimulates secretion of TSH by thyrotropes
Gonadotropin-releasing hormone (GnRH)	Single chain of 10 amino acids	Stimulates secretion of FSH and LH by gonadotropes
Corticotropin-releasing hormone (CRH)	Single chain of 41 amino acids	Stimulates secretion of ACTH by corticotropes
Growth hormone–releasing hormone (GHRH)	Single chain of 44 amino acids	Stimulates secretion of growth hormone by somatotropes
Growth hormone inhibitory hormone (somatostatin)	Single chain of 14 amino acids	Inhibits secretion of growth hormone by somatotropes
Prolactin-inhibiting hormone (PIH)	Dopamine (a catecholamine)	Inhibits secretion of prolactin by lactotropes

ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone.

Hormones of hypothamalus and immune system – cytokines stimulate secretion of CRH and somatostatine and inhibit secretion of TRH.

Hypophysis

- *Hypophysis cerebri, glandula pituitaria*
- oval extension at the end of infundibular part of the hypothalamus and is located in *sella turcica*
- Two parts adenohypophysis and neurohypophysis, they are connected with hypothalamus via stalk that goes through *diaphragma sellae*
- Hypothalamic-hypophysial portal blood vessels
- Adenohypophysis – ectodermal origin
  - Growth hormone (GH, somatotropin, STH)
  - Adrenocorticotropic hormone (ACTH)
  - Thyroid-stimulating hormone (TSH)
  - Prolactin (PRL)
  - Follicle-stimulating hormone (FSH)
  - Luteinizing hormone (LH)
- Neurohypophysis – neural origin, formed mainly by axones of hypothalamic neurons
  - antidiuretic hormone (ADH, vasopressin)
  - oxytocin (OXY)

Adenohypophysis

- Five different types of cells
- Production of hormones of adenohypophysis is regulated by hypothalamus:
  - Parvicellular neurons from various nuclei of hypothalamus
  - Axonal transport and termination in the area of *eminentia mediana* (median eminence)
  - Here are released and transported to the portal circulation (absence of HEB, fenestrations)
  - Production of hormones of adenohypophysis
    - pulse/cyclic activity
  - The quantitative representation of individual types of cells varies depending on the physiological / pathological conditions

Preproopiomelanocortin

- Corticotropes
- Large precursor protein (anterior and intermediate lobes of the pituitary gland)
- After cleavage of the signal peptide proopiomelanocortin is created
- Also lungs, gastrointestinal tract, placenta, hypothalamus
- Corticotropes:
  - ACTH and β-lipotropin and small amount of β-endorphin
- *Pars intermedia*:
  - CLIP, γ-LPH and β-endorphin
- Melanotropin
  - melanocytes
  - Receptors for melanotripin-1

Growth hormone (GH, somatotropin, STH)

- Chromosome 17
- *hGH-N*
  - „normal“, 75 % STH, Mr = 22000, 191 AMK
- *hGH-V*
  - „variant“
  - Mainly in placenta, 191 AAs, from the prior differs in 13 AAs, almost exclusively in the blood during pregnancy
- Significant variability of STH within species
- STH – binding with protein, which represents a fragment of the extracellular domain of receptor for STH
  - About 50% in bound form
  - Half time of about 6-20 min, the daily secretion 0.2 – 1.0 mg/day
  - Basal level about 3 ng/ml
  - Receptor – *GHR* gene
  - Mutations = Laron syndrome (dwarfism)
- JAK-STAT (signal transducers and activators of transcription)

Growth hormone (GH, somatotropin, STH)

- aglandotropic
- Induces growth of almost all tissues capable of growth (hypertrophy, mitosis)
  - Chondrocytes and osteogenic cells
  - Changes in conversion of chondrocytes to osteogenic cells = bone growth
- Specific metabolic effects
  - **Increased protein synthesis in almost all somatic cells** (in a few minutes) – mechanisms:
    - Increasing transport of AAs across biomembranes
    - Enhanced mRNA translation
    - Enhanced transcription to form DNA (24 to 48 h)
    - Reduction of the catabolism of amino acids, peptides and proteins
  - **Increased mobilization of fatty acids from adipose tissue** (several hours)
    - increasing their utilization as an energy source
    - Increased FA conversion to acetyl-CoA (energy metabolism)
    - Preference prior to proteins and sugars
    - Ketogenic effect
  - **Reduction of utilization of glucose and carbohydrates**
    - Reduced uptake of glucose (particularly in skeletal muscle, adipose tissue)
    - Increased hepatic glucose production
    - Increased secretion of insulin (diabetogenic effect) – GH induces „insulin resistence“

- increase in body weight; for increasing weight saccharides are essential together with insulin

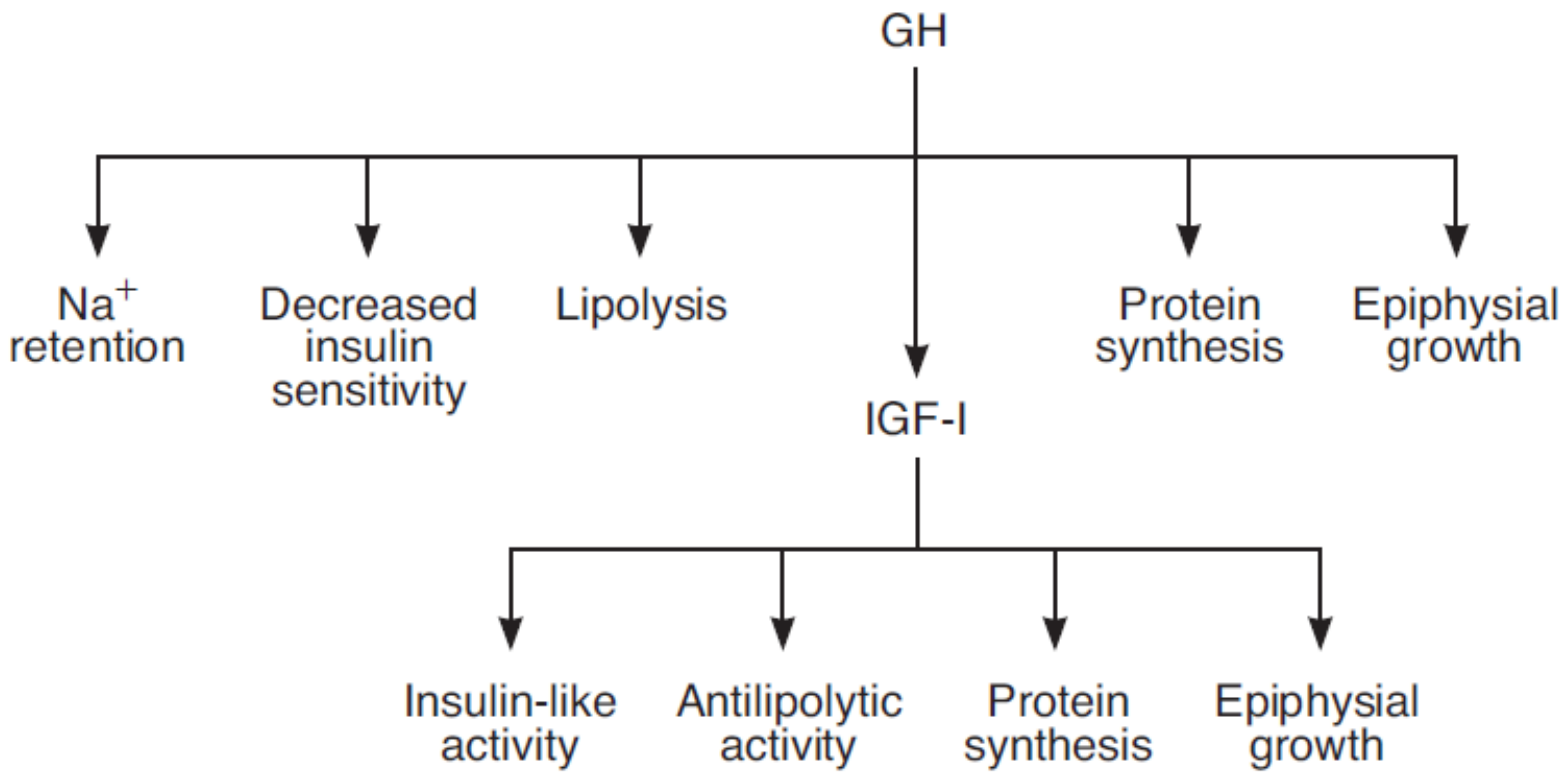


FIGURE 24–6 Actions believed to be mediated by growth hormone (GH) and IGF-I. (Courtesy of R Clark and N Gesundheit.)

Somatomedins

- The effect of growth hormone is mediated by somatomedins
- Their effect is often similar to the insulin = Insulin-like Growth Factors (IGF), the primary the structure highly homologous with insulin
- IGF-1 (somatomedin C) is produced by the liver as a result of stimulation by growth hormone; circulates in the blood bound to specific transporters
  - The most important, MW = 7500
  - Carrier proteins = half-time about 20 hours
  - Its concentration in the plasma closely follows the rate of GH secretion
  - Changes in expression of the gene found in many types of cancer
  - Important role in the process of cell proliferation and apoptosis
  - Pygmies - congenital genetic defect, lack of IGF-1
- IGF-2 – particularly important in ontogenetic development (pregnancy)
- Changes in expression in certain types of tumors

Plasma Level of IGF-1 as a Measure of Growth Hormone Secretion

The plasma concentration of IGF-1 is a valuable measure of GH secretion. The wide swings in plasma [GH] that result from the pulsatile secretion of this hormone have confounded efforts to use GH measurements to diagnose disorders of GH deficiency or excess. However, an increased circulating concentration of IGF-1 is one of the most useful clinical measures of the excess GH secretion that occurs in acromegaly (i.e., GH excess in adults) and gigantism (i.e., GH excess in children). Measurement of plasma [IGF-1] has also helped to explain the genesis of a particular type of dwarfism known as *Laron dwarfism.* These patients were initially identified as persons with growth failure mimicking that of typical pituitary dwarfism; however, plasma [GH] is normal or elevated, and treatment with GH is ineffective in reversing the growth failure. It was subsequently demonstrated that these individuals have mutations of their GH receptors that make the receptors nonfunctional. Thus, the mutant GH receptors cannot trigger the production of IGFs. With the availability of recombinant IGF-1, it is possible that effective treatment of these children will restore growth.

Despite the structural similarity of their receptors, IGF-1 and insulin exert different actions on tissues. IGF-1 has a more marked effect on growth, and insulin has a more significant effect on glucose and lipid metabolism. However, the differences in the postreceptor signaling pathways triggered by the two hormones have not been well defined.

The regulation of GH secretion

- During aging level of GH slowly decreases, at the age only 25 % of the values of adolescents
- Pulse secretion
- Some factors influencing GH secretion are probably dependent on nutrition
- Secretion is stimulated by:
  - Emotional effects (excitement)
  - Trauma
  - Ghrelin - controls the distribution and use of energy produced by ghrelin cells in the GIT
  - Effect of catecholamines, serotonin, histamine, GABA, cytokines
- Increased production is recorded during the first two hours of deep sleep
- Physiological level 1.6 – 3.0 $ng.mL^{-1}$, in children and adolescents up to 6.0 $ng.mL^{-1}$
- Increase up to 50.0 $ng.mL^{-1}$ during the shortage of proteins or carbohydrates in the diet

Guyton and Hall Textbook of Medical Physiology. 12th Ed. Elsevier 2006

Disorders of growth hormone secretion

- **Pituitary gigantism** (in children, unclosed growth plates - bone growth) – hyperglycaemia, degeneration of beta cells of the islet of Langerhans due to overactivity
- **Acromegaly** (adults, enlargement of acral parts, strengthening of bones, tendency to hyperglycemia and diabetes)
- **Pituitary disorders** (lack of growth hormone) – dwarfism, especially in children, poor growth, accumulation of abdominal fat, muscle tissue regression, increased risk of cardiovascular diseases and atherosclerosis
- **Laron syndrome** (areactive or missing receptors for growth hormone)
- Defects in production of IGF-1/2
- **Panhypopituitarism** –adulthood (tumorous conditions – craniopharyngiomas or chromophobe tumours, thrombosis of the adenohypophyseal blood vessels) – hypothyroidism, depressed production of glucocorticoids, supressed production of gonadotropic hormones

Anabolic-Androgenic Steroids

We are all unfortunately familiar with the potential for abuse of anabolic-androgenic steroids by bodybuilders and competitive athletes. Illicit use of these agents appears to be widespread in sports, where strength is closely linked to overall performance. In addition to naturally occurring androgens such as testosterone, dihydrotestosterone, androstenedione, and dehydroepiandrosterone, many different synthetic androgenic steroids—as well as GH—serve as performance enhancers. In addition to the sought after "beneficial" effects of increasing muscle mass and strength, each of these agents carries with it a plethora of adverse side effects. Some—such as oily skin, acne, and hair growth—are principally cosmetic. Others—including liver function abnormalities, mood changes with aggressive behavior, and hepatocellular carcinoma—are much more serious. Illicit use of these agents by younger athletes, especially teenagers, is also problematic with regard to alterations in growth and sexual maturation.

ACTH – adrenocorticotropic hormone

- Linear polypeptide, 39 AAs, POMC
- Inactivation *in vitro during* 10 min, place of inactivation unknown
- Increased glucocorticoid secretion
  - ACTH receptors (G protein)
  - Also osteoblasts, mechanism of action via VEGF that mediates survival of osteoblasts?
- Increasing the sensitivity of the adrenal gland to next doses of ACTH
- Secretion in irregular pulses = diurnal rhythm (suprachiasmatic nuclei of the hypothalamus)
- 25 pg/ml
- During stress, amount of ACTH secreted is rapidly stimulated via CRH

Prolactin (PRL)

- Protein consists of 198 AAs with three disulphide bones, MW = 22 500
- lactotropic cells of adenohypophysis, possible glycosylation (+/-)
- + thyreoliberin and VIP peptide, estrogens
- - dopamine (PIH – prolactin-inhibiting hormone)
- About half the level in men in comparison with women
  - High level of PRP = amenorrhea, anovulation associated with galactorrhea (women)
  - High level of PRP in men = decreased libido, impotence, oligospermia, involution of the prostate, decreased testosterone production
- Released (secreted) during sleep, but also under stress conditions
- + Pregnancy (20x increased)
- + Irritation of the nipples at breast-feeding

- Lactotropic effect:
  - + differentiation of the mammary gland during puberty
  - In pregnancy together with estrogens and progesterone stimulates enlargement and expansion of the alveoli and ducts of the mammary gland
  - + synthesis of casein and lactalbumin
- In men, it affects metabolism of testosterone and formation of androgen receptors
- Secreted during orgasm, the rate is proportional to the gratification and leads to short-term decrease in sexual appetite
- Probably only negligible effect on immune functions

Neurohypophysis - antidiuretic hormone (ADH)

- 9 AAs
- large cells of *nucleus paraventricularis* and *nucleus supraopticus*
  - precursor = signal peptide + ADH + neurophysin II + glycoprotein
  - ADH binds with neurophysin II – transport into neurohypophysis
  - Release into the blood
  - ADH synthesis is regulated by:
    - osmolarity of blood plasma (osmoreceptors in the anterior wall of the third ventricle, *n. supraopticus* and *n. paraventricularis;* magnocellular neurons)
      - Hyperosmotic stimulation
      - Hypoosmotic stimulation
    - Changes in circulating blood volume and blood pressure changes
      - Changes in blood pressure - baroreceptors (low-pressure in the atria of the heart, the high-pressure in *sinus caroticus* and *arcus aortae*)
  - ADH:
    - Increases the reabsorption of water
    - Vasoconstrictive action - influencing blood redistribution from skin, muscle, and intestinal areas into the brain and liver
    - Effect on memory – stimulates the formation and recall of memory traces

Neurohypophysis - oxytocin

- 9 AAs, from ADH differs in the 3th and 8th AA
- Precursor molecule is synthesized in the same parts as in the case of ADH
- + after distension of the cervix and uterus during labor
- after stimulation of the nipples, lactation
  - facilitating birth, maternal bonding - uterokinetic effect (use of oxytocin to induce labor), induces uterine contractions
  - milk ejection - contractions of myeloepithelial mammary cells and milk ejection
  - positive feedback mechanisms.
- Secreted also during orgasm
- Opposite effect on memory compared to ADH
  - inhibits the formation and recall of memory traces
- Role in the neuroanatomy of intimacy, specifically in sexual reproduction of both sexes, in particular during and after childbirth
- Intensively investigated in connection with:
  - Onthogenetical development of cardiomyocytes
  - Social behavior
  - Modulation of inflammation
  - Autism
  - Cognitive functions

MSH – melanocyte-stimulating hormone

- *Pars intermedia* of hypophyse
- Melanotropic cells (neurosecretory cells, + by corticotropin releasing hormone, thyrotropin releasing hormone, BDNF, urocortin, mesotocin, and vasopressin)
- Protein, three forms – alfa/beta/gama?
  - α-MSH: Ac-Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val
  - β-MSH: Ala-Glu-Lys-Lys-Asp-Glu-Gly-Pro-Tyr-Arg-Met-Glu-His-Phe-Arg-Trp-Gly-Ser-Pro-Pro-Lys-Asp
  - γ-MSH: Tyr-Val-Met-Gly-His-Phe-Arg-Trp-Asp-Arg-Phe-Gly
- Common sequence with corticotropin (ACTH) = common origin in pro-opiomelanocortine
- Its level rises during pregnancy = together with estrogens responsible for skin pigmentation in pregnant women
- Regulation of skin pigmentation in the absence of hormones of the adrenal cortex ?

- Note - synthetic analogues (afamelanotide - photoprotection, Melanotan II - increased libido, Bremelanotide - an aphrodisiac effect, both mediated by hypothalamic neurons expressing the melanocortin receptors MC3R and MC4R)

Thyroid gland

- *Glandula thyroidea*, weight approx 20 g.
- The thyroid gland is a butterfly-shaped organ, two cone-like lobes, *lobus dexter* (right lobe) and *lobus sinister* (left lobe), connected via the isthmus
- Each lobe is about 5 cm long, 3 cm wide and 2 cm thick
- The organ is situated on the anterior side of the neck, lying against and around the larynx and trachea, reaching posteriorly the esophagus and carotid sheath.
- Many closed spherical **follicles** (100 – 300 um in diameter) filled with secretory substance called **colloid** and lined with **cuboidal epithelial cells** that secrete into interior of follicle.
- The major constituent of colloid is glycoprotein **thyroglobulin**, which „contains“ thyroid hormones.
- Tissue with capillaries (with fenestration), nerves, and parafollicular (C-) cells are also present
- thyroxine (T4) and triiodotyronine (T3) are produced in cuboidal cells, calcitonin is created in parafollicular cells.

Thyroglobulin

- Glycoprotein (10 %), Mr = 660 000
- Two domains
- 123 tyrosine moieties
- Iodination of only 4 – 8 tyrosine moieties per 1 molecule!
- In blood serum 6 ng/ml, increased in hyperthyroidism / some forms of cancer (marker)
- Half-life 65 hours

Regulation of the synthesis of T3 and T4

- TSH (thyroid-stimulating hormone
  - Secretion of TSH is controlled by negative feedback by thyroid hormones,
  - TSH is simultaneously controlled by the hypothalamus (TRH, thyrotropin-releasing hormone - stimulation of the biosynthesis and secretion; TSH - inhibition)
- Thyroid hormones also simultaneously inhibits TRH
- TSH binds to membrane receptors on follicle cells - increase in the intracellular calcium ion concentration and the activation of adenylyl cyclase system
- uptake of iodide from blood increases
- thyroglobulin synthesis is stimulated as well as its proteolysis with consequent release of thyroid hormones into the blood
- Permanent stimulation of TSH - follicular cell hyperplasia, loss of colloid
- Decrease of stimulation - atrophy of follicular cells, the accumulation of colloid

- Cytokines stimulate the secretion of somatostatin and inhibit the secretion of TRH and response of thyroid gland to TSH
- (propylthiouracyl, methimazole, carbimazole - inhibition of the synthesis of T3 and T4 through the inhibition of the peroxidase)

TSH (Thyroid-stimulating hormone, from adenohypophysis)

- Glycoprotein with MW = 28 000
- Specific effects on thyroid gland:
  - Increased proteolysis of thyroglobulin = release of thyroid hormones into the blood
  - Increased activity of the iodide pump = increased uptake of iodine
  - Increased tyrosine iodination
  - Enlargement and increased in secretory activity of the thyroid cells
  - Increasing the number of these cells
- Controlled via TRH (thyrotropin-releasing hormone)
  - TRH transported to adenohypophysis
  - Direct stimulation of formation of TSH via activation of phospholipase system under increase in phospholipase C, second messengers (calcium ions, DAG), and finally increased TSH level occurs.
- TRH is also released as a result of other stimuli, eg. cold (activation of hypothalamic centers for thermoregulation)

Transport of T3 a T4 and their biological activities

- T3 and T4 circulated in blood bind with the suitable transport proteins (it makes pool)
  - TBG (thyroxine binding protein; globulin with electrophoretic mobility between α1- a α2-globulin), prealbumin (TBPA), and albumin
  - The amount of TBG in pregnancy increases due to the effect of estrogens

- Only very small active (= free) fraction (about 0.03 % of T4 and 0.3 % of T3)

- Upon entry into cells, T4 is deiodinated to T3 and total T3 binds with the nuclear receptors TR:
  - Two human *TR* genes: alpha-receptor gene on chromosome 17 and beta-receptor gene on chromosome 3
  - Alternative splicing to form two DIFFERENT receptor proteins
  - TRβ2 only in brain
  - TRα1 and TRα2, as well as TRβ1 in many tissues
  - Unclear function of TRα2 – it does not bind with T3

- Complex (monomers, homodimers, heterodimers with other nuclear receptors, mainly with a retinoid X receptor) then binds to DNA via zinc fingers and this process consequently leads to:
  - Stimulation or inhibition of the expression of several proteins (enzymes, membrane proteins, hormones)
  - Promoting growth and morphogenetic maturation of young body and stimulation of the metabolism (increase heat production under increased oxygen demand)
  - normal development of the nervous system, growth, and bone maturation (children, the need for substitution of genetically determined deficiency - risk of permanent mental damage)
  - Influence of activity of chondrocytes in the growth plates of bones
  - Positive chronotropic and inotropic effect (force of contraction), practically no effect on blood pressure, increased cardiac output (increasing the number of beta-adrenergic receptors)
  - Increased gastrointestinal motility
  - Stimulation of the synthesis of enzymes for gluconeogenesis (increased resorption of sugars from the digestive tract), lipolysis and proteolysis (ed. thyrotoxic myopathy, changes in expression of genes encoding MHC) and the associated changes in plasma levels of relevant hormones (eg. increased glucose metabolism = increased need for insulin secretion; similarly for parathyroid hormone, glucocorticoids)
  - Significant proteolysis of proteins of skeletal muscle, muscle tremors
  - Reduction of blood cholesterol levels independently on the increase in oxygen consumption
  - Stimulation and mobilization of fatty acids

- Thyroid hormones also have a "nongenomic" effects
  - Regulation of ion channels
  - Regulation of oxidative phosphorylation
  - Mediated by cAMP or protein kinases

Nongenomic effects of thyroid hormones

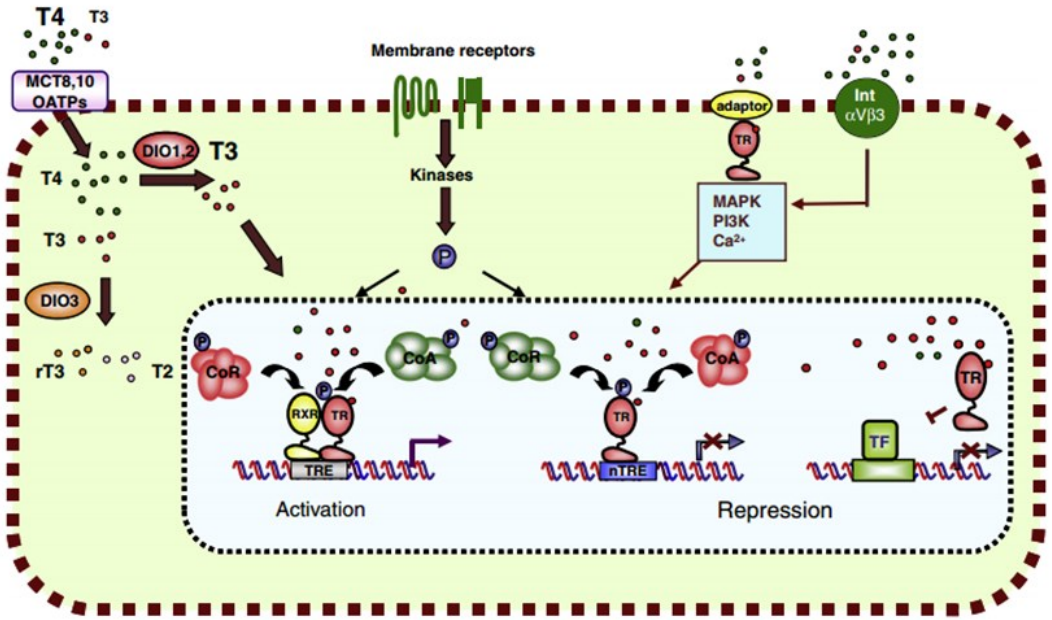


Fig. 1. Mechanism of action of the thyroid hormone receptors. Thyroxine (T4) and triiodothyronine (T3) enter the cell through transporter proteins such as MCT8 and 10 or OATPs. Inside the cells, deiodinases (DIO1,2) convert T4, the major form of thyroid hormone in the blood, to the more active form T3. DIO3 produces rT3 and T2 from T4 and T3, respectively. T3 binds to nuclear thyroid hormone receptors (TRs) that activate transcription by binding, generally as heterodimers with the retinoid X receptor (RXR), to thyroid hormone response elements (TREs) located in regulatory regions of target genes. Activity is regulated by an exchange of corepressor (CoR) and coactivator (CoA) complexes. Negative TREs (nTRE) can mediate ligand-dependent transcriptional repression, although in this case the role of coactivators and corepressors is not well defined. TRs can also regulate the activity of genes that do not contain a TRE through "cross-talk" with other transcription factors (TF) that stimulate target gene expression. Both receptors and coregulators are targets for phosphorylation (P) by signal transduction pathways stimulated by hormones and growth factors. Binding of T3 to a subpopulation of receptors located outside the nuclei can also cause rapid "non-genomic" effects through interaction with adaptor proteins, leading to stimulation of signaling pathways. T4 can also bind to putative membrane receptors such as integrin αVβ3 inducing mitogen activated protein kinase (MAPK) activity.

Table 1
Role of thyroid hormone receptors on proliferation and differentiation of selected cell types.

Cell type	Proliferation	Main receptor	Genes/pathways involved	Modulated biological response	Refs.
Hepatocytes	↑	TRβ	Cyclin D1	Liver hyperplasia* Liver regeneration* Regression of neoplastic nodules*	17-27
Hepatocarcinoma cells	↓	TRα, TRβ	PTTG1 Metastatic genes	Cellular invasion*,#	28-30
Pancreatic β -cells	↑	TRα, TRβ	Cyclin D1/CDK/Rb/E2F PI3K/AKT	Cell proliferation and survival*,#	31-33
Intestinal epithelial cells	↑	TRα	Wnt/β-catenin Notch, BMP	Intestinal maturation and renewal*	34-39
Cardiomyocytes	↑	TRα	MHC-α, ANF, SERCA2, β1-adrenergic receptors, K^+ channels PI3K/AKT	Contractility* Heart rate* Cardiac hypertrophy* Cardiomyocyte maturation#	40-57
Skeletal muscle cells	↓	TRα	MyoD and contractile genes	Contraction/relaxation* Myoblast differentiation#	58-64
Keratinocytes	↑	TRα, TRβ	Cyclin D1/CKIs p65/NF-κB, STAT3 Keratins	Epidermal proliferation and differentiation*,# Skin carcinogenesis*	65-73
Oligodendrocyte precursors	↓		Cyclin D1, c-Myc, CKIs	Oligodendrocyte maturation#	75-82
Neuroblastoma cells	↓	TRβ	Cyclin D1, c-Myc, CKIs	Morphological differentiation#	83-87
Photoreceptors		TRβ	Opsins	Retinal development* Color vision*	96-98
Cochlear cells		TRα, TRβ		Auditory function* Late differentiation of auditory cells*,#	99-103
Chondrocytes	↓	TRα,TRβ	CKIs Wnt/β-catenin, BMP Ihh, PTHrP, FGFR3	Endochondral ossification* Bone maturation*,# Mineralization*	104-117

TR action observed *in vivo* (*) or in cultured cells (#). Smaller letter size indicates less essential TR type.

Pascual A, Aranda A: **Thyroid hormone receptors, cell growth and differentiation.** ***Biochimica Et Biophysica Acta-General Subjects 2013, 1830(7):3908-3916.***

Hyperthyroidism:

High state of excitability, intolerance to heat, increased sweating, mild to extreme weight loss, varying degrees of diarrhea, muscle weakness, nervousness or other psychic disorders, extreme fatigue but inability to sleep, tremor of hands. EXOPHTALMUS (edematous changes of retro-orbital tissue, degenerative changes of the extraocular muscles, probably autoimmune process)

Hypothyroidism:

- Endemic colloid goiter caused by dietary iodide deficiency
- Idiopathic nontoxic colloid goiter
- Fatigue and extreme somnolence, extreme muscular sluggishness, slowed heart rate, decreased cardiac output, decreased blood volume, increased body weight, constipation, failure of many trophic functions, etc.

Clinical Assessment of Thyroid Function

Plasma thyrotropin levels. Direct measurements of T_4/T_3 provide a measure of *total* circulating hormone (i.e., the sum of *free* T_4 and T_3, as well as T_4 and T_3 *bound* to TBG, TTR, and albumin). However, these direct measurements do not allow one to distinguish between bound and free T_4/T_3. The sensitive response of TSH to changes in thyroid hormone levels provides an extremely valuable tool for assessing whether the free T_4/T_3 levels in the circulation are deficient, sufficient, or excessive. Indeed, the level of TSH reflects the amount of free, biologically active thyroid hormone in the target tissue. As a result, in recent years, measurements of plasma TSH using very sensitive immune assay methods have come to be regarded as the single best determinants of thyroid hormone status. Obviously, this approach is valid only if the thyrotrophs themselves are able to respond to T_3/T_4—that is, if patients have no evidence of pituitary dysfunction.

The health of the thyrotrophs themselves can be tested by injecting a bolus of synthetic TRH and monitoring changes in plasma [TSH]. In hypothyroid patients, the subsequent rise in plasma [TSH] is more dramatic than in physiologically normal individuals. This test was of great value in confirming the diagnosis of hypothyroidism before the advent of today's sensitive assays, but it has largely been abandoned.

Radioactive iodine uptake. Measuring the amount of a standard bolus of radioactive iodine that the thyroid can take up was also once widespread as a measure of thyroid function. A hyperactive gland would take up increased amounts of the tracer, whereas an underactive gland would take up subnormal amounts. Today, the test is mostly used for three other purposes. First, radioactive iodine uptake can show whether a solitary thyroid nodule, detected on physical examination, is "hot" (functioning) or "cold" (nonfunctioning). Cold nodules are more likely than hot ones to harbor a malignancy. Second, radioactive iodine uptake can show whether hyperthyroidism is the result of thyroid inflammation (i.e., thyroiditis), in which tracer uptake is minimal, or Graves disease, in which tracer uptake is increased. Third, high doses of radioactive iodine are commonly used to treat patients with hyperthyroidism.

The importance of iodine

- Adequate intake of iodine is essential for proper (correct) thyroid function
- Naturally, Mainly in coastal areas, less in mountain areas
- The daily requirement of iodine:
  - The first year of life 50 µg/day
  - 2 – 6 years 90 µg/day
  - 7 – 12 years 120 µg/day
  - 12 years and more 150 µg/day
  - Pregnant and nursing 250 µg/day
- Iodine deficiency leads to compensatory enlargement of the thyroid gland (struma)
- An excess of iodine - a reduction in uptake of iodine, reduction of thyroid
- Prophylaxis – enrichment of salt with KI
- Goitrogenic substances, especially crucifers with effect on iodine uptake

Iodine Deficiency

In areas where soil is relatively iodine deficient, human iodine deficiency is common. Because seawater and seafood contain large amounts of iodide, iodine deficiency is more common in inland areas, particularly in locales that rely on locally grown foods. For example, in inland areas of South America along the Andes Mountains, in central Africa, and in highland regions of Southeast Asia, iodine deficiency is common. In the early 1900s, investigators first recognized that iodide was present in high concentrations in the thyroid and that iodine deficiency promoted goiter formation. These observations led to efforts to supplement dietary iodine. Iodine deficiency causes thyroid hormone deficiency. The pituitary responds to this deficit by increasing the synthesis of thyrotropin (or TSH), which, in turn, increases the activity of the iodine-trapping mechanism in the follicular cell in an effort to overcome the deficiency. The increased TSH also exerts a trophic effect that increases the *size* of the thyroid gland. If this trophic effect persists for sufficient time, the result is an iodine-deficient **goiter**. The word *goiter* is simply a generic term for an enlarged thyroid. If this effort at compensation is not successful (i.e., if insufficient thyroid hormone levels persist), the person will develop signs and symptoms of goitrous **hypothyroidism**. When iodine deficiency occurs at critical developmental times in infancy, the effects on the CNS are particularly devastating and produce the syndrome known as **cretinism**. Persons so affected have a characteristic facial appearance and body habitus, as well as severe mental retardation. Dietary supplementation of iodine in salt and bread has all but eliminated iodine deficiency from North America. In many nations, especially in mountainous and landlocked regions of developing nations, iodine deficiency remains a major cause of preventable illness.